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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1926

ORIGINAL ARTICLES.

NEW DEVELOPMENTS IN OUR KNOWLEDGE OF THE GALL BLADDER.*

By Evarts A. Graham,

ST. LOUIS, MO.

(Department of Surgery, Washington University School of Medicine and Barnes Hospital.)

My appreciation of the high honor which you have bestowed on me in inviting me to give the second McArthur lecture of the Billings Foundation is only exceeded by the extreme pleasure afforded me in the opportunity to pay my respects to the distinguished surgeon for whom this lectureship was named, one who has enriched our profession not only by his contributions to surgical thought and to surgical art, but also by his example of high idealism and modest devotion to the truth. To the founder also, our beloved Dr. Frank Billings, I wish to pay my affectionate respects, for his early and unceasing support of scientific medicine in Chicago and the middle west, for his generosity in giving young men the opportunity to grow tall and for his own far-reaching scientific contributions to medical knowledge.

By the physiologist, the gall bladder is regarded as a reservoir and a concentrator of bile and as a regulator of pressures within the biliary system. To the clinician, this organ has been the subject of increasing interest and importance, until now it is recognized to be the most common organic cause of dyspeptic symptoms.

* McArthur Lecture of Billings Foundation delivered before Chicago Institute of Medicine and Chicago Surgical Society at Chicago, March 26, 1926.

During recent years the literature pertaining to cholecystitis has become so voluminous that it would be impossible even to summarize much of the important new knowledge on this subject. With your indulgence, therefore, I shall confine my remarks chiefly to those phases which have interested my associates and myself during the last few years.

Pathogenesis of Cholecystitis.—We are now perhaps just at the beginning of a rational conception of how inflammation of the gall bladder begins, of how it produces its symptoms and of what its effects are. In solving these questions the pathologists have given us scant help. Often even today, the gall bladder does not receive from the postmortem pathologist the close attention which it merits! Too often, on the other hand, the clinician has been prone to consider the gall bladder separately as an organ apart from others, forgetting that not only is it a part of the biliary system but that it is also a part of the much larger system of organs drained by the portal vein. Curiously enough, the cystic vein empties not into the hepatic veins but into the portal vein, so that the blood which has passed through the wall of the gall bladder is returned through the liver instead of into the vena cava directly. The significance of this anatomical arrangement is not yet understood, but it would seem to indicate that something of importance is formed in the gall bladder. Sweet[1] has produced evidence in favor of the formation of something by the gall bladder which helps to deësterize cholesterol esters.

For many years it has been recognized that cholecystitis may occur as a late sequel of typhoid fever, and surgeons have often commented on the fact that at operation for cholecystitis, a chronic appendicitis or a peptic ulcer may be found associated with a chronically inflamed gall bladder. Such findings led Birch-Hirschfeld in 1895 to conclude that cholecystitis is probably usually produced by bacteria which are carried to the liver, excreted into the bile and then pass into the lumen of the gall bladder. This idea of a contact infection of the mucous membrane seemed to be a sufficiently plausible explanation, but unfortunately for it Cushing[2] in 1899 showed that it is practically impossible to infect the mucous membrane of a normal gall bladder, at least in the dog, by the introduction of bacteria into its lumen. To produce a cholecystitis in this way it is necessary to injure the mucosa, to prevent emptying by ligation of the cystic duct, or to interfere with the blood supply. This finding has been confirmed by many others since Cushing published his experimental results. Morevoer, both Osler[3] and Rolleston[4] showed that cholecystitis is extremely rare during the acute course of a typhoid fever, even although it is known that at that time the bile is usually teeming with typhoid bacilli. Meyer, Neilson and Feusier[5] in 1921 showed also in their extensive experimental studies of paratyphoid infections that cholecystitis did not

occur unless there were actual inflammatory lesions in the liver in spite of the fact that in practically all of their animals the organisms could be found in the gall-bladder bile regardless of whether hepatic lesions were present or not. The evidence, therefore, seems overwhelming that the mere presence of pathogenic bacteria in the lumen of the gall bladder is not sufficient to induce cholecystitis.

In 1918 we[6] published the results of observations which indicated that also in man hepatitis is a constant accompaniment of cholecystitis. This fact was demonstrated by the microscopic examination of small pieces of liver tissue removed at operations for cholecystitis. The evidence of hepatitis consisted of a leukocytic infiltration of the interlobular or periportal tissue sometimes with polymorphonuclear leukocytes and at other times with round cells, depending upon the acuteness of the infection. It could be seen, however, that these infiltrations, while around the branches of the portal vein, were also around the small bile ducts and represented a pericholangitis. The constancy of this finding has been confirmed by many others; notably, for example, by Judd[7] and by Heyd, Killian and MacNeal.[8] It is important because it clearly demonstrates that inflammation of the gall bladder cannot be considered merely by itself but must always be considered as a part of a more extensive condition, namely an inflammation of the whole biliary system. It also is in entire agreement with the later findings of Meyer and his coworkers with regard to experimental paratyphoid cholecystitis in rabbits, to which reference has already been made.

In later publications, in association with Peterman and Priest, we[9] presented evidence which indicated that perhaps in a majority of cases cholecystitis is produced by a direct extension of inflammation from a liver already inflamed to the wall of the gall bladder. The extension of this inflammation can be shown experimentally to occur readily through the abundant lymphatic anastomosis which Sudler[10] in Mall's laboratory had already shown to exist between the liver and the gall bladder. The richest supply of lymphatic vessels in the gall bladder is situated immediately beneath the serosa. Therefore, cholecystitis which would occur secondarily to a hepatitis would be most likely to begin at the periphery of the gall bladder. This conclusion has been confirmed not only in experimentally produced cholecystitis but also in the findings which we have observed in the routine examination of gall bladders removed at operation. The early and less severe cases of cholecystitis almost invariably show the most inflammation at the periphery of the gall bladder and the least in the mucous membrane. Moreover, this conception of the pathogenesis of cholecystitis might also explain the frequency of vomiting as an early symptom, since peritoneal irritation would almost certainly occur early from the proximity of the lymphatic vessels to the peritoneal coat of the gall bladder. It would also be in harmony with the well-known fact that chole-

cytitis is frequently associated with other lesions of the portal system; as, for example, typhoid fever, peptic ulcer, appendicitis, and so forth. Other experiments have shown also that hepatitis will follow experimentally produced cholecystitis. The possibility of the establishment of a vicious circle between the liver and the gall bladder is therefore suggested whereby each may reinfect the other. It is not to be inferred from these conclusions that the opinion is held that all cases of cholecystitis are due solely to a lymphatic spread from a hepatitis. Some are doubtless due to hematogenous infections of the gall bladder as proposed by Rosenow,[11] although here also it is possible that some of his cases of cholecystitis experimentally produced by intravenous injections could be explained on the basis of a lymphatic transmission of the infection to the gall bladder from the liver. Some cases of cholecystitis also are doubtless due to involvement of the mucosa first and are therefore contact infections. These cases would be especially those in which foreign bodies (calculi) are present or in which perhaps an alleged stasis of bile might occur. This point has been rather extensively discussed by Seelig.[12] In view, however, of the extreme difficulty encountered in the experimental production of cholecystitis merely by the introduction of bacteria into the lumen of the gall bladder and also in view of the fact that in most cases of cholecystitis in the human the inflammation is seen to be most marked at the periphery and less marked in the mucosa, it seems reasonable to conclude that cases due to contact infection of the mucosa must be relatively few in number.

In our article of 1922[9] on the lymphatic orign of cholecystitis we made the statement that our experiments indicated that interstitial pancreatitis is also the result of a lymphatic spread of infection from the liver to the pancreas. This view had already been expressed by Deaver and Sweet[13] and had received support in the work of Maugeret.[14] It has been seriously questioned, however, by Archibald.[15] Recent unpublished work done in our laboratory by Kodama supports strongly Archibald's contention that the lymphatics from the region of the gall bladder pass along anterior to the pancreas but do not actually enter it. It is probable, therefore, that the cases of interstitial pancreatitis which we obtained following experimental hepatitis and cholecystitis were not due to a lymphatic spread but might have been due to a hematogenous infection. Kodama has shown, however, that if the gall bladder becomes adherent to the surface of the pancreas, then a direct anastomosis between the lymphatics of the gall bladder and those of the parenchyma of the pancreas exists.

Other important results of Kodama's study of the extrahepatic biliary lymphatics are as follows: When the superficial lymphatics of the first portion of the duodenum are injected with a solution of

trypan blue and gelatin the colored solution is found to enter the wall of the gall bladder through the lymphatic vessels which course along the common duct. If, however, the lymphatics of other portions of the duodenum, the second and third portions, are injected the colored solution does not enter the wall of the gall bladder but enters the mesenteric lymph gland which is situated at the beginning of the portal vein, after passing through the lymphatic vessels under the peritoneum between the duodenum and the portal vein. Conversely also, when the lymphatics of the gall bladder are injected, some of the colored solution passes into the lymphatics of the first portion of the duodenum. The possible bearing of these findings upon the association of cholecystitis and duodenal ulcer is obvious; and they suggest another method of pathogenesis of cholecystitis in addition to the one proposed above, which was that cholecystitis may follow a hepatitis, which in turn has resulted from infection brought to the liver by the portal vein from a lesion in the portal system. This work of Kodama's would indicate that a duodenal ulcer might induce cholecystitis directly by means of lymphatic extension without the intervention of a hepatitis. The constancy of the finding of a hepatitis in association with cholecystitis might then be due in some cases to an infection of the liver secondarily to the gall bladder. Kodama has also found that the lymph which comes from the liver, gall bladder, duodenum and first portion of the ascending colon always drains into the lymph gland which is located at the beginning of the portal vein. On the other hand, the lymph from the rest of the intestine is discharged into the various other mesenteric lymph glands.

It is felt, therefore, that by these studies new light has been thrown on the pathology and pathogenesis of cholecystitis.

Diagnosis. The diagnosis of typical cases of advanced biliary disease by the well-known clinical signs has been easy, but it is becoming more and more evident that the atypical and the early cases present such vague clinical evidence that many of them will be missed unless other diagnostic resources are utilized. In the majority of instances the clinical signs and symptoms are expressions of the late effects of disease. As in other conditions, however, it would be desirable to be able to make an early diagnosis at a time before these late effects have occurred. The procedure of Lyon[16] seemed to give promise of affording additional information which would be of diagnostic value. Unfortunately, however, since it deals at best only with the contents of the gall bladder, its value could be only inferential, since there is no assurance that either the mucous membrane or the bile is always altered in cases of cholecystitis, particularly in early cases. Moreover, as will be shown later, there is good evidence that the theory upon which the procedure is based (Meltzer's[17] idea of a reciprocal innervation between the

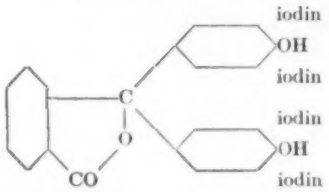
gall bladder and the sphincter of Oddi) is erroneous. At any rate, Lyon's test has not been found to be sufficiently accurate to come into general diagnostic use. It is only fair to state, however, that some observers are enthusiastic advocates of the method. The literature on both sides of the question was extensively reviewed in 1924 in an article by C. M. Jones.[18]

Equally disappointing also has been the use of tests to indicate a disturbed liver function as a means of diagnosing cholecystitis. In view of the constant association of a hepatitis with cholecystitis which was mentioned above, it seemed reasonable to hope that perhaps there might be a sufficient disturbance of liver function, even in early cases of cholecystitis, to permit its recognition by functional tests. In discussing this failure Gonzalez and Karr,[19] as well as others, have laid emphasis on the "large factor of safety of the liver which precludes the use of any functional test to detect minor disturbances of the organ." Furthermore, at best, any test based on a disturbed liver function would of necessity furnish only indirect evidence in the diagnosis of cholecystitis. A summary of the present status of tests of hepatic function has been made recently by C. H. Greene.[20]

Of all theoretical possibilities of laboratory aid, it would seem that the Roentgen ray would offer the most hope of providing additional help in the diagnosis of obscure cases of cholecystitis, if it were possible to see the gall bladder by this means, in a manner analogous to the revolutionary effects of the Roentgen ray in the diagnosis of lesions of the chest, of the alimentary tract, and other places. But here again, in the past, the Roentgen ray has been a disappointment for reasons which are well known. What was needed to make the Roentgen ray more efficient was a new principle which would be based on the idea of giving the patient some substance which, after getting into the gall bladder, would permit its visualization. Such a procedure, theoretically, should become as helpful in diagnosis, as pyelography or as the visualization of the stomach by means of the opaque meal.

It was such considerations as these which, in the summer of 1923, led Cole and me,[21] and later Copher, to investigate the possibilities of various substances in rendering the gall bladder visible. The work of Abel and Rowntree[22] in 1910 on the pharmacologic actions of some of the phthaleins and their derivatives showed that many of these were excreted in large part in the bile, and it formed the basis of the extensive use to which some of them have been put as a means of determining the functional capacity of the liver. With this work as a starting point it occurred to us that it might be possible to obtain Roentgen ray shadows of the gall bladder if substances were used which would contain a nucleus identical with, or closely allied to phenolphthalein with which iodin or bromin

atoms had been combined. The first substance which we used was tetraïodophenolphthalein of the following formula:



Both the free acid and the sodium salt were used. By the use of this substance it was demonstrated in dogs that cholecystography is possible by the intravenous injection of a substance which contains a phenolphthalein nucleus. It was also learned that the stomach and duodenum must be empty of food in order to obtain a satisfactory shadow of the gall bladder. Unfortunately, however, it happened that our first preparation contained toxic impurities which resulted in the death of some of our animals. Thinking at first that the toxic results were due, in part at least, to inevitable decomposition products of the iodin compound, we decided to try the tetrabromin products instead. By analogy with a well-known chemical fact that organic iodin compounds are usually less stable than the corresponding bromin compounds, we concluded that tetrabromphenolphthalein would probably be less toxic than tetraïodophenolphthalein. It was disappointing, however, to have to abandon temporarily the use of the latter because, theoretically, by virtue of the higher atomic weight of iodin, smaller doses of the tetraïodophenolphthalein should be required to produce good shadows; and apparently most of the toxicity of a pure product is due to the phenolphthalein radicle. Much of our early work, including the establishment of the criteria of interpretation of the cholecystograms, was therefore done with the sodium salt of tetrabromphenolphthalein, and our first publications on the principle of cholecystography were based largely on results obtained by the use of this substance.

In the summer of 1924, however, after various vicissitudes we were able to obtain some highly purified tetraïodophenolphthalein, and we learned that our former bad results in dogs were in large part due evidently to impurities which could be eliminated. This discovery permitted us to use the tetraïodo compound on the human subject with the gratifying result that relatively few toxic results occurred, when doses were employed which were only about half so large as those necessary to be used when the tetrabrom compound was given. Because, however, of our first experience in getting toxic effects with the tetraïodo compound, we desired to be extremely cautious in recommending its general use in the human until after the process of manufacture could be free from toxic impurities.

Whitaker and Milliken[23] of Boston, in January, 1925, reported their results obtained with a good sample and recommended that the iodin product should be used instead of the bromin. Their article appeared practically simultaneously with one of ours in which we reported the resumption of work with tetraïodophenolphthalein, but in which we were cautious in recommending its use because of marked differences in toxicity which we had noted in samples from different manufacturers and also because we were not certain of the stability of the substance on standing. These young men are entitled to credit for having gone ahead independently and on their own initiative in an attempt to improve the method of cholecystography and their article helped greatly to popularise the procedure. Gradually the iodin compound has almost entirely supplanted the tetrabromphenolphthalein. The use of the tetraïodo compound does not change in any way the standards of interpretation as worked out for the tetrabrom compound. Presumably the criteria of interpretation would be the same for any substance which would make the gall bladder opaque to the Roentgen ray. We have experimented with forty different substances, some of which had never been made before. Of these various substances, which we have mentioned in our publications, eleven have been found to have the power of making the gall bladder visible. But of these eleven there seem to be only three which are suitable for clinical use. These are tetrabromphenolphthalein, tetraïodophenolphthalein, and the isomeric compound of the latter, phenoltetraïodophthalein.

Both tetrabromphenolphthalein and tetraïodophenolphthalein are secreted almost entirely by the bile, as high as 97 per cent, as shown experimentally in the dog. Neither colors the serum, but recently we have found that the isomeric compound of the latter, namely phenoltetraïodophthalein not only produces good gall-bladder shadows but also colors the serum sufficiently after alkalinization of it to make it possible to employ it as a test of hepatic function in a manner similar to the Rosenthal test with phenol-tetrachlorphthalein. Therefore, by those who place confidence in the diagnostic value of tests of hepatic function, this substance may be used simultaneously for cholecystography and for tests of hepatic function. It also colors the urine after alkalinization, but since about 98 per cent is secreted in the bile and only 2 per cent in the urine, it will probably not be of much value as a test of renal function. We are still experimenting with this substance and we are not yet prepared to state its final value.* It will probably afford an excellent opportunity to compare accurately the relative values

* Since the preparation of this manuscript we have found that sodium phenol-tetraïodophthalein possesses so many advantages over the other two substances for intravenous use that we now use it routinely instead of the others. It can be given in smaller doses, with consequently less chance of a toxic reaction, and because of its more rapid excretion through the liver the period of examination may be shortened.

of cholecystography and hepatic functional tests in the diagnosis of disorders of the biliary tract.

In order to understand the interpretation and the value of cholecystography in diagnosis it is necessary to consider some of the theoretical points involved in its use. The substance employed must be excreted by the liver into the bile. It must pass with the bile into the gall bladder where it must be concentrated by the absorption of water in order to give the densest shadows. It is obvious, therefore, that the densest shadows will be found in normal subjects. It is equally apparent that there may be no shadow at all or only a faint one, if the liver is unable to excrete the substance normally, if the cystic duct is occluded or if the gall bladder is unable to concentrate its contents because of a diseased wall. Moreover, as bile is poured out from the gall bladder into the common duct, it is obvious that the shadow will diminish in size and gradually disappear altogether. Since the presence of food in the duodenum is accompanied by an outpouring of bile, the necessity of fasting during the period of concentration of the substance in the gall bladder becomes evident. It is seen therefore that cholecystography is really a means of studying the function of the gall bladder rather than an indication of the exact pathologic lesions present.

The sodium salt of tetraïodophenolphthalein is readily soluble in water and may be administered either intravenously or by mouth. Our own preference is for the intravenous method. Three or 3½ grams are dissolved in from 30 to 50 cc. of water, filtered and sterilized in a boiling water bath for fifteen minutes. Or it may be given in still greater dilution. The solution is injected in the morning between 8 and 9 A.M., preferably in two equal doses, a half-hour apart. Dividing the dose tends to eliminate any chance of reaction to the injection, although recently serious reactions have practically disappeared. Breakfast is omitted. For lunch the patient may have a liquid diet low in protein and fat. Roentgenograms are made four, eight and twenty-four hours after the injection. A series of Roentgenograms is essential in order to gain information concerning the concentrating function and the ability of the gall bladder to empty itself. An important modification of this procedure has been suggested by Milliken and Whitaker[24] who give a meal containing fat in order to determine the ability of the gall bladder to reduce its size promptly. This is based on important work by Boyden[25] to which reference will be made later. Case[26] gives his injections at 5 P.M. in one dose, dissolved in 75 to 100 cc. of Ringer's solution. Films are taken before breakfast. The patient then eats a meal including egg yolk or milk and cream and he returns at about noon for more films which conclude the examination. Pribram, Gruenberg and Strauss[27] have recommended the use of a preliminary injection of pituitrin in an attempt to empty the gall bladder.

The oral method of administration was first recommended by

Menees and Robinson[28] of Grand Rapids. In our own early work we had observed that cholecystograms could be obtained after oral administration of these substances but we did not recommend the procedure for clinical use because we felt that it was bound to be less accurate than the intravenous method. It is necessary that any of these substances should be protected against the action of the gastric juice, because the hydrochloric acid of the stomach converts the soluble sodium salt into the insoluble free acid which will then not be absorbed. For purposes of protection various capsules and coatings have been devised. An excellent discussion of this whole subject of oral administration is given by Levyn and Aaron,[29] who have carried on extensive experiments with various kinds of protective coatings. I cannot enter into an extensive discussion of the various methods of giving the substances by mouth, but I should like particularly to call attention to the articles on this subject by Whitaker, Milliken and Vogt,[30] by Stewart, Einhorn and Ryan[31] and by Larimore,[32] in addition to the one by Levyn and Aaron. In general, in using the oral method, a slightly larger dose is used than by the intravenous method, the capsules are given after the evening meal and the patient presents himself before breakfast for his first film. A meal is then taken, preferably one rich in fats, and other films are made about four hours later and on about the twenty-fourth, thirty-sixth and forty-eighth hour afterward, if the shadow still persists.

There is no doubt that the oral method would offer advantages over the intravenous method if it should prove to be equally reliable. It seems unlikely to us, however, that it can ever be made so reliable because of uncertainty concerning the amount which has been absorbed. Some workers have combined the two methods by utilizing the oral method first and following it by an intravenous administration if there is any doubt about the interpretation of the films. In this way fewer patients will need to be subjected to the intravenous injections.

The principal reason for considering the oral method has been the fear of toxic reactions. We feel that these fears are practically groundless, since more highly purified products can now be obtained from the manufacturers. We have personal knowledge of about 10,000 patients in various parts of the world who have received intravenous injections and we have heard of no deaths which could be ascribed to the injection. Case states that in 600 cases of his own examined by the intravenous method, the reactions have been limited to 2 or 3 per cent and these have consisted only of nausea and vomiting. This is a smaller percentage than that ordinarily reported by those who use the oral methods. Pribram has even reported using the intravenous method in cases of acute yellow atrophy of the liver without serious consequences. We, however,

do not advise its use in such cases. Our own experience with toxic reactions has been as follows:

In the last 150 cases examined by the use of sodium tetraïodophenolphthalein there has been no case in which any alarming reaction has occurred. In 2 cases, however, the first injection was followed by reactions of sufficient severity to make it seem wise to withhold the second injection. If, however, every possible symptom that might be regarded as a reaction is considered, including such events as transient flushing, transient headache or dizziness, which sometimes last for only a minute, then we find that of 100 cases of intravenous injection 65 per cent are affected. It is very doubtful, however, how many of these are real effects and how many are imaginary, since the patients were asked to note carefully effects of any kind. Case's excellent results in regard to reactions would indicate that perhaps his method of administration is superior to ours. Still more interesting to us is the fact that in this series of 150 cases the 48 cases examined by the oral method had 70 per cent of reactions as judged by the above standard; and of this number 48 per cent had some degree of nausea or vomiting as compared with only 22 per cent after the intravenous method.

Another objection sometimes offered against the intravenous method is the danger of thrombophlebitis at the site of injection. We have found that this danger can be completely obviated by washing out the vein with a little saline solution immediately after the injection. If a little extravasation into the tissues occurs because of difficulty encountered with a very fat arm, heat should be applied for several days.

The interpretation of abnormal shadows requires experience with the method, as in any other diagnostic procedure; but it has been surprising to us how quickly the interpretation has been mastered by all those who have published their experiences, sometimes even with a small number of cases. From various parts of Europe as well as from this country and South America the published reports have all stated that by means of the method a correct diagnosis has been made in 90, or more than 90, per cent of cases. The chief points in making the diagnosis of cholecystic disease are: (1) Failure to obtain a shadow when the technique has been properly carried out. We agree with Carman[33] in his statement based on a study of 1100 cases that a failure to obtain a shadow is unexcelled in diagnostic value. (2) Filling defects. Soft calculi which are otherwise invisible frequently are seen in the cholecystograms as "negative" shadows, or filling defects. They occupy space in the gall bladder which would otherwise be filled with the opaque substance. Many small stones often produce a mottled appearance, which is very characteristic. (3) Irregularities of contour, denoting adhesions, diverticula, etc. (4) Variations from the normal in density of shadow, in the time of appearance and disappearance of

the shadow. These last criteria are more difficult points to interpret than the former, and they constitute most of the 4 to 10 per cent of failures in diagnosis encountered by various observers at the present time. Other difficulties of interpretation have been encountered in certain cases of hepatic enlargement of unknown etiology.

Up to March 23, 1926, we had employed the method in 900 cases, in which 653 received one of the dyes intravenously, 245 orally and 2 per rectum. In the last year and a half we have used almost entirely the sodium salt of tetraïodophenolphthalein. Of this number 109 had their gall bladders removed, all of which were subjected to microscopic examination. In only 3 of these cases was the Roentgen ray diagnosis not confirmed. In other words, the Roentgen ray diagnosis was found to be correct in 97.2 per cent of cases in which there was an opportunity to verify it by microscopic examination of the gall bladder. In accuracy of diagnosis, therefore, we feel that this method compares favorably with any other diagnostic method for any other condition. We agree with Sherwood Moore[34] that cholecystography is a more accurate method of diagnosing cholecystic disease than inspection and palpation of the organ at operation. Because it is a functional test of the gall bladder it discloses abnormality in very early and mild cases of cholecystitis, perhaps even before structural pathological changes are visible.

Physiological Considerations. As we predicted in one of our early articles the method has proved useful not only in diagnosis but also in adding new knowledge to the physiology of the gall bladder. Until recently there has apparently been no serious question raised against the commonly accepted idea that the gall bladder empties itself by a contraction of its wall in a manner similar to the emptying of the urinary bladder or to a peristaltic wave of the intestine. In 1917, Meltzer,[17] proposed his theory of a reciprocal innervation between the sphincter of Oddi and the gall bladder, which had as its basis the idea that simultaneously with the relaxation of the sphincter there was a contraction wave of the gall bladder. This idea has also been the foundation upon which has rested the Meltzer-Lyon procedure for the so-called nonsurgical drainage of the gall bladder. Within recent years, however, numerous doubts have been expressed as to the correctness of this conception. Sweet has seriously questioned whether or not bile ever passes out of the gall bladder through the cystic duct, and he has emphasized both the anatomical features of the cystic duct which would offer mechanical obstacles to the outlet of bile from the gall bladder and the marked absorptive ability of its wall which has been emphasized by Rous and McMaster.[35] Halpert[36] also has raised similar questions. Even the existence of a true sphincter at the ampulla, or at least of its effectiveness, has been questioned by Carlson,[37] Burget[38] and others. Finally also much evidence has been submitted to show that no demonstrable peristaltic action of the

muscle of the gall bladder ever occurs. These questions have interested my associates and myself and I shall take the liberty of summarizing some of the work which has appeared recently and some of which has not yet been published.

Concerning the question of whether or not the bile from the gall bladder passes out through the cystic duct, the evidence derived from cholecystographic studies shows in a very convincing manner that it does. Boyden[25] and also Sosman, Whitaker and Edson[39] have shown that a fat meal, especially one containing egg yolk and cream, has the power of reducing the gall bladder shadow to about one-tenth of its former size within the brief time of one hour and forty-five minutes. It is difficult to think of any other mechanism to explain this sudden diminution than an outpouring of bile through the cystic duct. Certainly there is no apparent reason why such a meal should suddenly lead to a very great increase in the rate of absorption of bile from the gall bladder. Incidentally, also, this simple procedure is very much more effective in emptying the gall bladder than the more complicated one of using magnesium sulphate by the Meltzer-Lyon method. Copher and Kodama,[40] in our laboratory, have found that oleic acid when placed in the duodenum is even more potent in this respect. Additional evidence that bile passes out through the cystic duct is derived from the finding of the thick dark gall bladder bile by the Lyon procedure. Another striking demonstration is afforded in the experiment of Copher's,[41] already published, which showed that if the common bile duct of a dog is ligated before an injection of the tetraïodo compound, the shadow of the gall bladder will remain indefinitely regardless of diet or other factors. In one case, for example, it remained for three weeks, after wich the dog was killed for examination.

As regards the question of the presence of a sphincter such as described by Oddi, Copher and Kodama have found that a distinct sphincter cannot always be found apart from the fibers of the muscle coat of the intestine. They considered that normal tonus of the duodenal wall might be an important factor in the resistance to the flow of bile into the duodenum, because they observed discharges of bile from the duodenal papilla coincidentally with duodenal peristaltic movements. While they were experimenting further with this point, Burget published his observations which led him to conclude that undue importance has been attached to the sphincter of the common duct, that resistance to pressure in the common duct is offered by the normal tonus of the duodenum and that peristalsis of the duodenum is an important factor in emptying the duct by a milking action and by aspiration due to reduced pressure following a peristaltic wave. Carlson offered no experimental proof for his opinion that the tonus of the wall of the duodenum is more important than the so-called sphincter of Oddi. It is a well established fact, as stated in Quain's Anatomy,[42] that the human

common bile duct together with the pancreatic duct perforates the muscular wall of the duodenum and runs obliquely for 2 or 3 cm. between the coats to form an elevation beneath the mucous membrane. In most instances it opens by a common orifice with the pancreatic duct near the junction of the second and third portion of the duodenum. In the dog also the common bile duct runs for a distance of from 2 to 4 cm. obliquely through the wall of the intestine before it enters the lumen. Copher and Kodama, in work not yet published, have shown that this anatomic arrangement constitutes a sphincter-like mechanism which is dependent upon the tonicity of the intestine and makes it possible for intestinal peristalsis to be a factor in regulating the flow of bile from the common duct. Their experiments were designed to measure simultaneously, not only the changes of pressure in the common duct and in a segment of duodenum, but also the amount of contents discharged from each. They found that the discharge of the contents of the common bile duct into the duodenum takes place during the relaxation phase of a duodenal peristaltic movement, regardless of whether the duodenal peristalsis is spontaneous or induced by chemical, thermal, mechanical or electrical stimuli. Comparatively little change of pressure in the common duct was noted after the introduction into the duodenum of magnesium sulphate even in concentrations of 25 to 50 per cent. A variety of drugs and other factors were tested in this way. Pituitrin, for example, was found to produce an initial immediate relaxation of the duodenum and a marked fall in the common duct pressure with discharge of its contents. The pituitrin, however, quickly increases the tonus and activity of the intestine. The marked effect of oleic acid has already been mentioned above. The relaxation of intestinal tonus was found to be an equally important factor in the emptying of the pancreatic duct. In the light of these experiments, therefore, it seems unnecessary to assign much importance to the so-called sphincter of Oddi.

Most of the work on the outflow of bile into the intestine has been done with experiments dealing directly with the duodenum or with the ampulla of Vater. Cole,[43] however, last year published the results of his experiments done in our laboratory which showed conclusively that the introduction of alkali into the stomach caused a marked inhibition of the outpouring of bile into the duodenum, even when the pylorus was securely ligated to prevent the escape of any of the alkali into the duodenum. The most marked results were obtained when from 75 to 150 cc. of 0.5 per cent sodium hydroxide were introduced into the stomach of the dog. The explanation of this phenomenon is not entirely clear.

Concerning the third question raised, namely, how the gall bladder empties itself, certain facts stand out conspicuously. If it is emptied by a contraction similar to a peristaltic wave, it would seem that such a wave would have been seen so frequently as to leave no room

for doubt. But, on the contrary, no one has ever seen the gall bladder contract, except Matsuo[48] who claims to have seen one gall bladder contract during an abdominal operation. Surgeons have long been familiar with the fact that mechanical stimuli which frequently induce peristalsis in the intestine or stomach never cause a similar response in this organ. Thus, the gall bladder can be pinched with a clamp, incised with a knife or touched with a cautery without the least evidence of a contraction wave similar to peristalsis. Cholecystography ought to present an ideal method for observing peristaltic waves if any occur. But we and many others have watched patiently for them with the fluoroscope without ever having seen the slightest evidence of their occurrence. Moreover, Boyden and Whitaker[25] have found (and we have confirmed this observation) that an electrical stimulation which is sufficient to produce violent contraction waves in the intestine or urinary bladder elicits no demonstrable response at all when applied to the gall bladder. How then does it empty itself?

Before attempting to answer this question it will be well to state that no one has ever observed a gall bladder that is completely empty. It will also be well to examine the structure of the gall bladder itself. Sweet, Mann[44] and others have commented on the relatively poor musculature of this organ. Boyden states, "the muscularis of the intestine is considerably thicker than that of the gall bladder, the difference being far greater than appears, since the fibers in the intestine are so much more closely packed" but "the connective-tissue layer of the gall bladder is nearly three times as thick as that of the intestine and, as stained with resorcin-fuchsin, is evidently much richer in elastic tissue; this tissue is surely an important factor in the mechanics of the gall bladder." Some movements of the gall bladder have been observed by Bainbridge and Dale[45] and others, but under conditions which leave uncertainty as to whether the factor of pressure by respiratory movements was satisfactorily excluded. As a matter of fact, Copher and Kodama have observed rhythmic movements in an artificial gall bladder made by substituting a small rubber bag for the gall bladder in a dog. The force of intraäbdominal pressure aided by respiratory and other movements, has been invoked by Winkelstein[46] to explain the process of emptying. In this connection an interesting fact which Boyden mentions is that "Diemerbroeck in 1672 saw in the pressure of the full stomach the timely agent for evacuating the gall bladder when its contents would be most needed." Boyden himself regards the gall bladder chiefly as a passive structure, from a mechanical viewpoint, except for the elasticity of its wall. The evidence at hand seems greatly to favor this view. When the gall bladder is examined immediately after a sudden reduction in size from a fat meal it is found to be not a contracted organ with a circular lumen on cross section but to be

flabby with an irregularly-shaped lumen. If a contraction wave had emptied the organ, one might expect to find a circular lumen.

Copher and Kodama have recently performed some crucial experiments, not yet published, which can leave little doubt that whatever active muscular contraction there may be, it can at most play only a minor role in the emptying of the gall bladder. The chief factors in its emptying are purely passive and are explained on simple mechanical principles, as follows: The gall bladder is a distensible viscus which responds to increased pressures in the common duct by becoming distended. When the ductal pressure is suddenly lowered by a sudden opening of the intestinal end of the duct there is an elastic recoil on the part of the wall of the gall bladder which results in the ejection of bile from the organ. Also, as the bile is streaming down the common duct past the orifice of the cystic duct there may be some siphonage action in a manner analogous to that of the filter pump well-known to chemists, although the Heisterian valves may interfere somewhat with the exit of bile in this way. The intermittent sudden opening and sudden closing of the duodenal end of the common duct results, therefore, in a gradual washing out of the gall bladder. But obviously the gall bladder can never be entirely empty. Copher has shown that if daily injections of the tetraïodo compound be given to a dog, a shadow of the gall bladder remains throughout the entire period of experiment. This shows conclusively that the gall bladder is never empty, at least during the period of the experiment. The intermittent opening and closing of the duodenal end of the common duct is in turn dependent chiefly upon the state of contraction of the wall of the duodenum. Kodama has devised a model to illustrate the filling and emptying of the gall bladder based on these principles, and a description of it will appear in the June number of the *American Journal of Physiology*. If now these conceptions are correct then it should be possible to substitute in the living dog an artificial, elastic gall bladder which would act like a normal gall bladder in emptying and filling. Such was found to be the case. The gall bladder was removed from a normal dog and a small rubber bag was connected with the cystic duct. By using cholecystographic examination with the aid of tetraïodophenolphthalein it was found that this rubber gall bladder behaved like a normal one, except that of course there was no ability to concentrate the bile by absorption of water. A longer time also was required for the disappearance of the shadow than is the case in the normal animal, due perhaps to the fact that the elasticity of the rubber bag was not quite the same as that of the gall bladder. In another experiment the artificial gall bladder was encased in a celloidin protector to prevent the influence of intraäbdominal pressure. In this experiment also the rubber bag, after an intravenous injection of tetraïodophenolphthalein, became gradually visualized, and the shadow

gradually disappeared, although the time of disappearance was even longer than when intraäbdominal pressure was allowed to play its rôle. We believe that the chief function of the gall bladder is to maintain tonus and to prevent overdistension.

This work therefore leaves little rational basis for the conception of Meltzer of a reciprocal innervation between the socalled sphincter of Oddi and the gall bladder. Moreover, if one imagines that he can empty the gall bladder by a single application of magnesium sulphate to the papilla of Vater, he has no experimental evidence to substantiate his opinion, although Silverman and Menville have obtained cholecystographic evidence of a reduction in size of the gall bladder after the use of magnesium sulphate. If, however, he desires to empty the gall bladder in some such manner, he will find that the simple device of giving a meal of egg yolk and cream will more nearly empty it with less discomfort to the patient than will the application of magnesium sulphate through a duodenal tube.

I have purposely avoided a discussion of many other phases of the physiology and pathology of the gall bladder and the bearing of all these experimental results upon the treatment of cholecystitis because it is impossible to cover adequately within the space of one lecture the many apects of this interesting organ.

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THE CAUSES AND TREATMENT OF HIGH BLOOD PRESSURE.*

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Does high blood pressure represent a disease entity or is it a symptom perhaps of several disease states? Is it in origin inherently metabolic, degenerative or infectious? What relation does it bear to chronic nephritis? Is the one dependent upon the other or both upon a common cause? And what is its relation to arteriosclerosis? Assuredly they are related, but which comes first? These questions and many more suggest themselves.

The belief that vascular hypertension starts with renal impairment has much to support it. Major for instance has shown that in this disease guanidin is excreted by the kidney with difficulty, and conversely that this substance when injected into normal animals will invariably raise the blood pressure. His work would suggest that retention of this or some related substance produces first of all hypertension, and that, as a part of the same process, there later appears obvious kidney disease. The fact that uninterrupted hypertension progresses always to evident nephritis lends further support to this view.

On the other hand, the suggestion has repeatedly been made that the initial change of hypertension is an atherosclerosis of the

* Discussion held (in the Moving Picture Theater) at the Dallas, (1926) Meeting of the American Medical Association.

smaller organ arterioles and that this subsequently calls forth, as a compensatory measure, increased blood pressure—a degenerative process inherent to the individual. Aschoff has shown that even at the age of thirty-five years, or earlier, degeneration of the intima begins and that this is apt to be progressive. This theory has much to recommend it, but it cannot explain every case of hypertension.

Then too, consider the influence of nervous tension and the hurried life, full of excitement, which in some people seems to be clearly related to high blood pressure. It is conceivable that emotional strain leads to such disturbance of vasomotor control as to produce, first, temporary and passing high blood pressure, and later, permanent hypertension. There is good reason for believing that neurovascular constriction, long continued, may cause such changes in the vessel wall as to bring about permanent hypertension. It is not necessary to assume that emotional influences alone are responsible; chemical bodies, the result of metabolic disturbance, acting upon the vasomotor centers can conceivably produce the same chronic vascular constriction and the same train of troubles. There is good evidence in support of this.

Effort has been made to associate hypertension with endocrine disturbance. The frequency with which it occurs in fat people would suggest some such relationship.

We have discussed several theories, each of which has something to recommend it. There are as many more. It is indeed possible that back of it all is some underlying cause or group of causes which we have not yet touched upon. There is one cause of arterial hypertension, however, about which we need not theorize—heredity, or better, constitutional predisposition. The relationship is clear. Often we encounter a family, all of whom, parents, brothers and sisters, show cardiovascular disease or have died of some form of it. Just how heredity acts, whether it handicaps these people through early arterial degeneration, through an imbalance of neurovascular control, through some abnormality of metabolism, or in some yet undreamed of manner, it is impossible today to say. Its predominating influence, however, is evident.

Today, then we must regard high blood pressure merely as a disease complex, often inherited, in which hypertension is the salient clinical feature, the exact pathogenesis of which is unknown but which in its later stages is accompanied by disease of the kidneys, myocardium and arteries.

There are various types: The person who is comfortable and without symptoms; the obese woman, who, with few or no symptoms develops hypertension about the time of the menopause; the thin patient of the same age who complains of cardiac palpitation and of various nervous troubles; the highly neurotic person sometimes fat, sometimes thin; the business man who lives under high tension, is intense in his feelings and in the way he meets his

problems; and finally the youthful individual whose fulminant illness runs a rapidly fatal course.

For simplicity's sake the following classification may be adopted: (1) Early hypertension; (2) chronic hypertension without nephritis, so-called essential hypertension; (3) chronic hypertension with nephritis; (4) fulminant hypertension.

The patients of the first group have few or no subjective symptoms; systolic pressure is not high and, what is still more important, is not constantly increased, and the diastolic pressure is not elevated. There is no evidence of arteriosclerosis or nephritis and the disease responds, sometimes permanently, to treatment.

The second type shows high systolic pressure, 200 or more, with a relatively low diastolic pressure, 100 or less; there may be cardiac hypertrophy and arteriosclerosis. Dizziness, headache, irritability and easy exhaustion are complained of. The urine is approximately normal, and there is normal blood chemistry. Progress of the disease may be arrested, it may gradually go into nephritis, or it may end in some vascular accident or in cardiac failure.

The third type shows high systolic and especially high diastolic pressures. The symptoms above noted are marked and to these may be added angina, myocardial limitation, retinal hemorrhages, and loss of mental acuity. The urine shows the changes of chronic nephritis and the blood toward the end contains a high percentage of urea and creatinin. These patients last only a few years. Cerebral hemorrhage, angina or uremia may carry them away.

The fourth type is rare but is the most malignant. Ushered in by headache, insomnia and irritability, with great elevation of both systolic and diastolic pressures, it soon gives evidence of marked renal impairment. The outcome is foreshadowed by a low 'phthalein output, and high blood urea and creatinin. Intellectual deterioration, headaches, profound retinal changes, and other evidences of uremia quickly appear. Within a few weeks or months the patient dies in uremic coma; less often through some vascular accident. I know of nothing more surely fatal, not even sarcoma.

The treatment of arterial hypertension though sometimes fruitless, will often accomplish much. True, for patients with long-standing hypertension and pronounced changes in arteries, heart and kidneys, we can do little else than temporize and postpone the inevitable; but for those whose illness is of shorter duration and who present less obvious organ changes, we can accomplish a great deal.

Manner of living counts most. Oftentimes it is best to initiate treatment by putting the patient to bed for three or four weeks. Give him absolute rest, mental and physical. Convince him when he gets out of bed that he has reached the crossroads; that the pathway he chooses and the rate he travels will determine his fate. His entire manner of living must be reviewed and carefully revised.

Sufficient relaxation, mental and physical, and regular hours for sleep, rest and play, all should be insisted upon. Frequent vacations are essential; week ends away from work are good. If it is a woman the details must be changed to meet the exigencies of her situation. Fewer parties and less excitement; or with another type, less household drudgery. The underlying principle in every instance is the same: more frequent and more complete mental and physical relaxation. One rule should apply to every patient almost without exception: he should lie down in a room alone for one hour after the midday meal.

Diet is of great importance, but I doubt if in the average case it is entitled to the place of predominating influence often accorded it. High blood pressure is not primarily a kidney disease and unless renal impairment is evident there is no reason to restrict the patient's diet to such an extent as to materially lower his nutritive efficiency. Why tell a man with good kidneys that he must eat no meat? It must be admitted that the abuse of protein can work harm, sometimes disaster, and because of the hazards ahead of him the patient with hypertension should never be permitted an excessive protein intake. If, however, kidney function is good as evidenced by an approximately normal urine, normal blood chemistry, little or no increase in night urine, and no fixation of specific gravity—if all of this obtains—then the patient should by all means be permitted sufficient protein to meet his physiologic needs, say, for the average man about 75 gm. daily, oftentimes a little more. If on the other hand, there is evidence of kidney impairment, this amount should be reduced somewhat, say to 50 or 60 gm. If there are signs of impending disaster, such as a 'phthalein output of 25 per cent or less, blood urea of 50 mg. or more, and blood creatinin approaching 5 mg., then the daily protein restriction should be more drastic, say 30 or 40 gm.

The patient should, within limits, be permitted to choose the kind of protein he finds most agreeable. The end products of protein metabolism are the same whether they come from milk, meat, eggs or cereal, and, gram for gram, the protein of meat imposes no greater burden upon metabolism than does that of milk or cereal. For our present purposes, there is not the slightest difference between red and white meats.

Regarding salt restriction I cannot agree with Allen, that chlorid retention is a predominating feature of this disease or that it is in large measure responsible for the continued hypertension. This author advises a "salt-free diet," one in which all food, even the bread, is prepared without salt (about 0.5 gm. daily). It is recognized that excessive amounts of sodium chlorid may do harm. After studying this question, however, upon a limited group of well-controlled patients, I am convinced that there is no special virtue in the salt-free diet of Allen, and that the usual "salt-poor"

one which contains the equivalent of about 2 gm. of sodium chlorid daily, accomplishes just as much. Others have reached similar conclusions. It is sufficient, I believe, to tell the patient that he must eat no unusually salty food, must take his butter unsalted, and must add no salt to his food after it reaches the table.

The correction of obesity is often an essential feature of the treatment. Many of these patients show marked lowering of blood pressure and experience amelioration of symptoms, when the weight is reduced. This should be accomplished by means of a subcaloric diet, say 15 to 20 per cent below the calculated normal. Often it is sufficient to tell the moderately obese patient that he must cut in half his accustomed allowance of bread and that he must eat no butter. Thyroid substance is always a two-edged sword which should be handled with caution, but it is sometimes of value. I have seen hypertensive obese individuals with a subnormal basal metabolism markedly improved through a combination of restricted diet and the cautious use of thyroid substance.

In regard to the other dietary factors, the patient should be permitted a fairly wide range of choice. The food should be simple, easily digested and never excessive in amount. There should be no highly seasoned foods, and no condiments. Coffee and tea should be limited and alcohol absolutely interdicted. Some milk, an abundance of fruits, and a liberal amount of green vegetables should be insisted upon.

The removal of all foci of infection is an important part of the treatment of hypertension. Teeth which show apical abscesses, and diseased tonsils, as well as other infected foci, should be removed. It should be emphasized, however, that this should not be carried to the point of extracting teeth which are merely devitalized. There can be little doubt that infection sometimes plays a role in the processes which lead to hypertension, but unfortunately our attention is seldom directed to the search for infection until irreparable damage has long since been done. Therefore, we should not expect to accomplish a great deal by removing foci of infection from patients with well-developed chronic hypertension.

The hazards to be met in this disease are threefold: Renal, cardiac and arterial. When disaster threatens, the treatment must be addressed to the source from which the danger comes. Impending uremia can often be aborted by venesection; not less than 600 cc. of blood, often more, should be taken. This is not a measure of permanent benefit but it will often tide the patient over a critical period and save his life. Sweating and purgation come next in importance.

Angina pectoris and myocardial failure should be treated with rest and other appropriate measures; high blood pressure is no contraindication to the use of digitalis. Chloral in small doses seems at times to have a very happy effect in relieving restlessness

and insomnia and permitting relaxation. Even in those patients who are not in immediate danger, the good effect of chloral often justifies its use; it is distinctly superior to bromides. At times, in the distress of myocardial failure, morphin is the only drug which gives relief.

In closing I want to say a word regarding liver extract. We have at times, though not invariably, seen a material drop in both systolic and diastolic pressure follow immediately upon the injection of these extracts. The duration of this reduction has varied from a few hours to several days. There has sometimes occurred amelioration of headache which had not responded to other measures. In a few instances certain disagreeable sensations, including mild shock, were produced. Viewed over a period of several weeks, however, the administration of liver extract has not appeared to us to have a lasting effect upon blood pressure. It should be added that our experience is too limited to warrant far reaching conclusions.

HYPERTENSION IN ITS RELATIONSHIP TO MITRAL STENOSIS AND AORTIC INSUFFICIENCY.

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1. **Mitral Stenosis.** Having noted a rather frequent association between mitral stenosis and hypertension in patients observed in the wards of Montefiore Hospital, it has seemed worth while to study this relationship in a little greater detail. We discovered that 29 per cent of patients with mitral stenosis, uncomplicated by other valvular lesions, who were discharged from Montefiore Hospital between January 1, 1922, and December 31, 1925, had high blood pressures (Table I). The textbooks and periodical literature give very little information on this point. In the days before sphygmomanometry became a clinical method, a number of observers had noted an association between granular kidneys and mitral stenosis. The granular or primary contracted kidney is the end result of long standing disease of the renal arterioles, which results in gradual focal destruction of glomeruli and tubules with connective-tissue replacement. It is now quite generally agreed that this arteriolar disease is secondary to long-continued arterial hypertension or else conditioned by the same factors that cause the

hypertension. It is a legitimate deduction, therefore, that granular kidneys with arteriolosclerosis found at necropsy give objective evidence that the blood pressure was elevated during the life of the subject.[1]

As early as 1857, Bamberger had insisted on the frequent association of slightly granular kidneys with valvular heart disease, and had characterized the renal picture as that of early Bright's disease.[2] His views were hotly contested by Traube, who believed that Bright's disease was only rarely associated with valvular heart disease, and that the lesions studied by Bamberger did not represent those of chronic Bright's disease. Goodhart[3] in 1880 described the frequent occurrence of granular kidneys in patients with mitral thickening, as well as with mitral stenosis, although his statistics as to the actual incidence are not quite clear. He believed that the valvular thickening and stenosis were different stages of the same process, and were consequent on a long standing relative mitral insufficiency secondary to the kidney disease. Seven years later Pitt,[4] surveying a large necropsy material, reported that in women one-third, and in men one-fifth of the fatal cases of mitral stenosis were associated with granular kidneys. Thirty-three per cent of his 115 autopsied cases of mitral stenosis had granular kidneys. On the other hand, of 542 cases with granular kidneys, 33 or 6 per cent had mitral stenosis, while only 2 per cent of the whole series of necropsies at Guy's Hospital showed mitral stenosis. More recently Cowan and Fleming[5] published similar findings, but their report is not quite clear, for they speak of "mitral disease," and of "kidneys more or less fibroid, with surfaces more or less granular." All but one of their cases were over fifty years of age. They believe that in patients with mitral stenosis and a negative rheumatic history the renal lesion is the cause of the cardiac one, and that the latter must be attributed to arteriosclerosis and to chronic nephritis. They conclude with the statement that the blood pressure in mitral stenosis is often above the average, and that the existence of hypertension suggests the presence of renal fibrosis. Gibson[6] and Coombs[7] have noted the common occurrence of high arterial pressure in patients with mitral stenosis. The former believes that these cases are nonrheumatic and that the valvular lesion is determined by a process similar to the one causing the renal disease, while the latter regards the hypertension as due to kidney disease, which was established by the rheumatic infection or by scarlatina.

Huchard[8] established a special syndrome which he called "le rétrécissement mitral des arteriosclereux." He believed that the valvular lesion was atherosclerotic in nature and since he identified hypertension and arteriosclerosis he explained the association of mitral stenosis and hypertension by assuming a common origin for both conditions. He pointed out that the characteristic clinical picture of mitral stenosis was often masked by the associated pres-

ence of hypertension in the greater circulation which might give rise to great left ventricular hypertrophy, accentuation of the aortic second sound, and peripheral arteriosclerosis. As has been suggested by one of us,[9] he was undoubtedly too sweeping in his conclusions and included many cases of rheumatic mitral stenosis in his arteriosclerotic category.

For the purpose of this study a systolic pressure over 150 and a diastolic pressure over 90 mm. of mercury was taken as an indication of hypertension. In children the standards of normal and abnormal blood pressure were taken proportionately lower, corresponding to published tables.[10] Only patients in whom the diagnosis of mitral stenosis was unequivocal were included in this first series, and all cases giving physical signs of aortic valvular disease were excluded.

During the four years covered by this study, 135 patients were discharged from or died at Montefiore Hospital with the diagnosis of mitral stenosis uncomplicated by aortic disease (Table I). Of these 39, or 29 per cent had hypertension. Hypertension was much more common in women than in men with mitral stenosis, and in the group of patients with both conditions 69 per cent were women. This sex distribution corresponds closely with that in uncomplicated hypertension. Of a series of 236 consecutive uncomplicated cases of essential hypertension, two-thirds were women. Except in 5 cases, hypertension associated with mitral stenosis occurred in patients over forty years of age.

TABLE I.—CASES OF MITRAL STENOSIS AND HYPERTENSION CLASSIFIED ACCORDING TO AGE AND SEX.

Age.	Number of Cases of Mitral Stenosis.					
	Male.		Female.		Both sexes.	
	Total.	With hypertension.	Total.	With hypertension.	Total.	With hypertension.
1 to 10 . . .	5	0	3	0	8	0
11 to 20 . . .	12	1	12	0	24	1
21 to 30 . . .	2	0	4	1	6	1
31 to 40 . . .	19	1	11	2	30	3
41 to 50 . . .	8	4	13	6	21	10
51 to 60 . . .	9	3	20	11	29	14
Over 60	5	3	12	7	17	10
Totals . . .	60	12	75	27	135	39

The close parallelism of sex and age distribution between the group of cases under study and those with essential hypertension, suggests that the association of mitral stenosis and hypertension may be merely an accidental one. Several facts speak against this

assumption. Of the 68 cases of mitral stenosis under forty years of age 7 per cent exhibited hypertension, while of 67 cases above forty, 55 per cent had an elevated blood pressure. Such a great frequency of hypertension cannot be due to chance. Moreover during the same four-year period 3778 cases of all types, exclusive of pulmonary tuberculosis, were discharged from the hospital and of these only 413 or 11 per cent had hypertension, giving a frequency of hypertension in the general hospital population only one-third of that among patients with mitral stenosis. Furthermore, of 403 patients with hypertension discharged from the hospital between January 1, 1922, and March 1, 1926, 34 or 8.4 per cent had mitral stenosis as well. It is interesting to compare our figures with those of Pitt, who found granular kidneys (hypertension) in 33 per cent of autopsied cases with mitral stenosis, and 6 per cent of mitral stenosis in a series of 542 necropsies showing granular kidneys. This correspondence supports the accuracy of our clinical diagnoses.

In an effort to explain these findings, we have studied our material from several angles. It is notoriously difficult to determine in any given patient the age at which the lesion of mitral stenosis first appeared. The date of onset of a rheumatic infection gives no clue, and even this often cannot be ascertained with accuracy. We have, therefore, signalized the onset of disease in our patients by the date of appearance of cardiac symptoms, such as breathlessness, palpitation, and edema. As is apparent from Table II, the incidence of hypertension bears no relationship to the duration of symptoms of cardiac insufficiency.

TABLE II.—DURATION OF CARDIAC SYMPTOMS IN PATIENTS WITH MITRAL STENOSIS AND HYPERTENSION.

Duration of symptoms (yrs.)	None	First	2	3	4	5	6–10	11–20
Number of patients . .	6	13	5	0	3	1	7	4

Twenty-five years ago, Sahli[11] described an elevation of blood pressure in patients with cardiac insufficiency, followed by a recession to normal with the recovery of cardiac function. This phenomenon, which he termed "Hochdruckstauung," was later described by Lang[12] and his students, who pointed out that it occurs particularly in patients with mitral disease and with pulmonary emphysema. In our experience such a transient rise in blood pressure with cardiac failure is quite unusual. This is confirmed by Frehse,[13] who was unable to observe this phenomenon in a series of 700 patients with cardiac insufficiency. The findings of the above-mentioned authors are probably explained by the fact that they did not allow for the normal variability in blood pressure, and did not obtain readings of residual or basal blood pressure. Table III, in which our cases are grouped according to

the state of their cardiac function, shows that of 135 cases of mitral stenosis, 70 or 52 per cent were decompensated, while of the 39 cases complicated by hypertension, 25 or 64 per cent were decompensated. Such figures indicate that cardiac failure does not play a determining role in causing hypertension in these patients. It is interesting to note that hypotension as evidenced by a systolic pressure in adults below 100 occurred in only 4 of the 135 patients with mitral stenosis.

TABLE III.—CASES OF MITRAL STENOSIS AND HYPERTENSION CLASSIFIED ACCORDING TO STATE OF COMPENSATION.

	With normal blood pressure.		With hypertension.		All cases.	
	Total.	Decompensated.	Total.	Decompensated.	Total.	Decompensated.
Number of patients	96	45	39	25	135	70

It is usually stated in textbooks on physical diagnosis that the radial pulse is of small volume in patients with mitral stenosis. This carries the implication to most readers that the pulse pressure is correspondingly small. Classifying pulse pressures below 30 as small, and those above 60 as large, we find that 95 of our 135 cases fall within normal limits, 38 are greater than normal and only 6 are small. The small volume of the pulse is probably to be explained, therefore, not by a small pulse pressure but rather by a great state of contraction or tone of the radial artery, which would give the same impression to the palpating finger.

During the four-year period 18 patients with mitral stenosis came to necropsy. The findings are detailed in Table VII. One case of mitral stenosis and hypertension which died in 1926 has been included in this table, although it does not appear in the other statistical compilations. It is apparent that there is a close correlation between the presence or absence of granular or arteriolosclerotic kidneys and the blood pressure. The patients with normal blood pressure had smooth, those with hypertension, granular kidneys. Undoubtedly the arteriolar disease is associated with the elevated blood pressure and has the same significance as in patients without valvular disease.[1] The lack of correlation between heart weight and blood pressure is explained by the varying influence of the different degrees of valvular defects. There is no relationship between the degree of stenosis of the mitral valve and the blood pressure.

In view of the opinions expressed by other authors that in the cases under discussion the mitral lesion is of atherosclerotic origin,

or possibly caused by the kidney disease, it has seemed worth while to study the etiologic factor in the development of the valvular disease in our patients. Sixty per cent of those with normal blood pressures, and only 28 per cent of those with hypertension gave a history of articular rheumatism, chorea, or sore throats. In evaluating these figures it must, however, be borne in mind that two-thirds of all patients with a rheumatic history were under forty years of age, and that only 13 per cent of all of the patients with hypertension were younger than forty. It is well known that in patients in the older age groups a history of rheumatic infection is uncommon, due in part to the hand of oblivion which time passes over the recollection of minor illnesses, and in part, undoubtedly to the fact that, as a rule, a clear history of rheumatic disease indicates that the patient has passed through a more serious and more generalized infection which is apt to cripple the heart to a sufficient degree to result in death before middle life. It seems that in older patients with valvular disease the infection is more indolent and takes a longer time to produce symptoms of functional disturbance. Turning to our necropsy material it appears that in the 11 cases with hypertension 10 presented lesions of rheumatic mitral disease while in only 1 was the stenosis of atherosclerotic origin. This patient was aged eighty-three years. Moreover, we have seen a few cases of mitral stenosis with normal blood pressure, which proved to be of atherosclerotic origin at autopsy.

TABLE IV.—CASES OF UNCOMPLICATED AORTIC INSUFFICIENCY AND HYPERTENSION CLASSIFIED ACCORDING TO AGE AND ETIOLOGY.

Age.	Syphilitic.		Rheumatic.		Atherosclerotic.		All causes.	
	Total.	With hypertension.	Total.	With hypertension.	Total.	With hypertension.	Total	With hypertension.
Below 40 . .	3	0	11	0	0	0	14	0
Above 40 . .	19	3	8	3	19	10	46	16
Totals . .	22	3	19	3	19	10	60	16

Hypertension, therefore, may be associated with mitral stenosis of either rheumatic or atherosclerotic origin, and its development probably bears no causal relationship to the agent responsible for the mitral stenosis. Hypertension is certainly not the cause of the mitral disease, for we have seen it develop after the narrowing of the auriculoventricular orifice had already been well established. An explanation may possibly be found in the reaction of the vasomotor center. As Starling[14] has recently again pointed out, a persistent high blood pressure indicates that at normal pressure the the circle of Willis is not receiving sufficient blood, for the brain and

vasomotor center require a constant supply of oxygen at high tension and they maintain an adequate arterial pressure whatever the needs of the other tissues. It has been shown that, in mitral stenosis, the minute volume flow may be considerably reduced and it is quite conceivable that this results in a peripheral vasoconstriction to maintain an adequate blood supply to the brain. The resultant blood pressure would be determined by the interplay of several forces, the strength of cardiac contraction, the amount of blood passing through the constricted mitral orifice into the arterial system, and the degree of vasoconstriction. The conditions are too complex to allow of a clinical solution.

TABLE V.—CASES OF COMBINED MITRAL STENOSIS AND AORTIC INSUFFICIENCY CLASSIFIED ACCORDING TO AGE AND SEX.

Age.	Male.		Female.		Both sexes.	
	Total.	With hypertension.	Total.	With hypertension.	Total.	With hypertension.
Below 15	12	0	7	0	19	0
15 to 40	16	0	17	1	33	1
Above 40	11	2	12	3	23	5
Totals	39	2	36	4	75	6

It has been suggested that the renal fibrosis is the result of long-standing passive congestion of the kidneys, but pathologists today agree that Traube was right fifty years ago in his contention that chronic cyanosis of the kidney does not result in granular atrophy.[15] We believe that the granular kidneys are the result of arteriolar disease following long-standing hypertension. Marked hypertension, or granular kidneys, according to this theory, therefore, point to a long duration of the mitral obstruction.

2. **Aortic Insufficiency.** There are many references in medical literature on the association of aortic insufficiency and granular kidneys. Thus Vaquez,[16] in his textbook, states that granular kidneys are found chiefly in aortic and rarely in mitral disease and that they are due to a general vascular sclerosis. Romberg,[17] too, says that granular kidneys are common with aortic disease and that these patients are characterized clinically by an increased mean blood pressure and a systolic pressure over 200 mm. of mercury. Several French observers[18] point out that marked hypertension in patients with aortic insufficiency always points to renal involvement, and that this combination is common in syphilitic and atherosclerotic aortic insufficiency but very rare in the type due to rheumatism. Cabot[19] has made a similar observation. MacDonald[20] found renal fibrosis at necropsy in 25 of 32 cases of un-

complicated aortic disease and in 18 of 22 cases of combined aortic and mitral disease.

TABLE VI.—CASES OF VALVULAR DISEASE WITH HYPERTENSION.

No.	Sex.	Age.	Etiology.	Blood-pressure.		Duration of symptoms in years.	Auricular fibrillation.	Remarks.
				Systolic.	Diastolic.			
				MITRAL STENOSIS.				
12736	M.	20	R	152	74	4	+	Decompensated.
13128	F.	26	R	140	108	4	+	Decompensated.
8433	F.	35	R	155	90	2	+	Decompensated.
8511	F.	37	R	150	80	10	+	Compensated.
11159	M.	37	R	190	110	6	+	Decompensated.
13139	F.	48	R	155	110	1½	−	Decompensated.
12405	F.	44	R	182	130	½	−	Compensated.
11464	M.	45	R	236	150	0	+	Compensated.
11442	F.	49	R	160	90	14	−	Compensated.
11427	F.	44	R	160	80	7	−	Slight decompensation.
11845	M.	47	R	160	95	16	+	Compensated.
12543	F.	46	R	150	105	1	+	Decompensated.
8367	M.	44	R	204	100	2	−	Decompensated.
12766	M.	45	R	228	125	½	+	Compensated.
12474	F.	47	R	145	95	0	−	Compensated.
8822	F.	56	R	214	114	14	+	Decompensated.
8888	M.	53	R	180	90	1	+	Compensated.
9049	F.	54	R	155	70	4	+	Decompensated.
9621	F.	56	R	180	130	5	−	Decompensated.
8482	M.	56	R	170	80	11	−	Decompensated.
10545	F.	55	R	160	60	1	+	Decompensated.
10527	F.	60	R	160	90	6	+	Slight decompensation.
10445	F.	52	R	164	98	4	+	Decompensated.
10433	F.	53	R	186	98	1	+	Decompensated.
13177	F.	57	R	152	95	1½	+	Decompensated.
11245	F.	55	R	180	100	0	−	Compensated.
10683	F.	53	R	270	120	10	+	Decompensated.
10642R	M.	60	R	195	90	6	+	Decompensated.
10566	F.	54	R	230	140	½	−	Decompensated.
13118	F.	65	R	158	84	½	+	Compensated.
11480	M.	69	R	156	98	1	−	Slight decompensation.
11653	F.	82	A	154	80	1	−	Compensated.
10772	M.	62	A	184	110	?	+	Decompensated.
10537	F.	62	A	152	88	½	−	Compensated.
10332	F.	68	A	180	110	½	−	Compensated.
9972	F.	72	A	175	80	0	−	Compensated.
9774	F.	66	A	160	90	?	+	Decompensated.
9330	F.	83	A	220	140	½	−	Decompensated.
8899	M.	64	A	210	140	½	+	Compensated.
				UNCOMPLICATED AORTIC INSUFFICIENCY.				
B. F.	F.	43	S	260	120	½	−	Compensated.
S. R.	M.	48	S	268	62	½	−	Compensated.
9756	M.	52	S	180	110	4	−	Compensated—C.S.Lues
10344	F.	55	R	175	95	5	+	Compensated.
01512	M.	61	R	200	120	?	−	Decompensated.
12160	F.	68	R	185	90	?	−	Decompensated.
12105	M.	55	A	230	140	5	−	Decompensated.
11588	M.	57	A	224	122	½	−	Decompensated.
10325	M.	54	A	215	115	1	−	Decompensated.
10164	M.	54	A	200	125	15	−	Compensated.
8533	F.	50	A	190	105	0	−	Compensated.
Vol. L	F.	55	A	195	150	?	−	Decompensated.
03001	M.	59	A	140	100	?	−	Compensated + Aortic stenosis.
11895	F.	65	A	195	105	2	−	Decompensated.
9083	M.	69	A	190	90	½	+	Decompensated.
10452	F.	87	A	204	108	½	+	Decompensated.
				MITRAL STENOSIS AND AORTIC INSUFFICIENCY				
11538	M.	65	S	196	100	?	−	Compensated.
10296	F.	16	R	235	150	12	−	Compensated + aortic stenosis.
10671	F.	42	R	185	128	11	+	Decompensated.
10102	F.	56	R	176	90	2	−	Slight decompensation.
12261	M.	56	R	180	100	3	+	Decompensated.
10042	F.	52	R	180	90	½	−	Compensated.

S = Syphilitic.
R = Rheumatic.
A = Atherosclerotic.

TABLE VII.—NECROPSY FINDINGS IN PATIENTS WITH VALVULAR DISEASE AND HYPERTENSION.

No.	Age.	Etiology.	Blood-pressure.		Heart weight in grams.	No. of fingers admitted by mitral orifice.	Kidneys.			Remarks.
			Systolic.	Diastolic.			Weight of both in grams.	Surface.	Arteriolosclerosis.	
						UNCOMPLICATED MITRAL STENOSIS.				
9104R	17	R	104	62	550	2 –	300	Smooth	–	
10808	18	R	120	60	810	2	810	Smooth	±	
9232	39	R	120	70	510	1 –	250	Multiple infarcts	+	
8128	34	R	100	70	300	1	340	Smooth	±	
12543	46	R	150	105	350	1	220	Multiple infarcts; slightly granular	++	
9348	44	R	140	72	400	1	200	Smooth, thin cortex	±	Chronic glomerular nephritis.
8367	44	R	204	100	640	1	310	Slightly granular	++	
13419	45	R	220	130	460	2	180	Granular	++++	
11118	53	R	122	85	500	slit	380	Smooth	±	
10636	56	R	150	95	400	1	300	Smooth	±	
8822	56	R	214	114	550	slit	280	Granular	+ to ++	
9621	56	R	180	130	420	1 –	300	Granular	++	
8000R	58	R	100	60	650	2	300	Slightly granular	+	
8482	56	R	170	80	500	1 –	250	Slightly granular	+ to ++	
13177	57	R	174	108	620	2 –	400	Finely granular	++	
10642R	60	R	220	100	?	1 –	?	Granular	?	
13118	65	R	158	84	400	1	320	Finely granular	+	
9330	83	A	220	140	400	2 –	210	Granular	++	

					Uncomplicated Aortic Insufficiency.					
10076	40	S	130	70	530	...	250	Moderately granular	+	
0478	50	S	170	?	580	...	340	Finely granular	++	
04049	66	S	110	65	260	...	200	Smooth	−	
0757	63	S	195	?	660	...	310	Smooth	No sections	
9826	26	R	146	50	570	...	360	Smooth	−	
8160	27	R	110	35	1000	...	320	Smooth	−	Aortic stenosis.
12502	40	R	134	48	800	...	240	Smooth	±	
01861	58	R	190	30	880	...	330	Smooth	−	
01512	61	R	200	120	580	...	600	Granular	+++	Glomerular nephritis.
12105	55	A	230	140	880	...	Small contracted	Granular	++++	Aortic involvement very slight.
Vol. L	55	A	195	150	540	...	300	Smooth	−	
03001	59	A	140	100	200	...	160	Granular	+++	Aortic stenosis.
01017	77	A	145	80	600	...	300	Slightly granular	No sections	Aortic stenosis.
10452	87	A	204	108	420	...	200	Granular	+	Very slight atheroma of aortic valve.
					Mitral Stenosis + Aortic Insufficiency.					
12162R	20	R	130	47	600	3 −	240	Smooth	−	
8330R	31	R	132	54	530	...	250	Smooth	−	Tricuspid stenosis.
8657	37	R	170	80	340	1	300	Smooth	−	
8129	55	R	110	60	600	1 −	340	Finely granular	−	
9449	54	R	120	70	600	1 −	300	Slightly granular	+	
11118	53	R	122	85	500	slit	380	Smooth	−	Aortic stenosis.
11631	68	A	125	75	210	1	230	Finely granular	+	
11136	68	A	142	66	220	?	220	Smooth	−	

R = Rheumatic. S = Syphilitic. A = Arteriosclerotic.

We have been able to collect 60 cases of uncomplicated aortic insufficiency from the records of Montefiore Hospital of the past four years. Sixteen, or 27 per cent of these had hypertension. No comparison of the sexes is possible, for in the whole series there were only 13 women. In Table IV the material is classified according to the age of the patient and the etiology of the valvular lesion. Hypertension occurred only in patients forty years of age or older. It was relatively uncommon in the rheumatic and syphilitic group, but half of the patients with atherosclerotic aortic insufficiency had an associated hypertension. We believe, however, that in this last group of cases the relationship of the valvular lesion and the high blood pressure is different than in all of the other groups. With rheumatic disease of the mitral or aortic valve, or with syphilitic valvulitis of the semilunar cusps, it seems quite evident that the elevated blood pressure cannot be a cause of the valvular lesion. It seems, however, that the hypertension is primary in many of the patients with atherosclerotic aortic insufficiency, and that the excessive strain which it places on aortic cusps which have undergone some degree of atherosclerosis determines the leak through the valve. In these patients, therefore, the aortic insufficiency is but a complication of an essential hypertension, and so they are not comparable to the patients with primary valvular disease. If we eliminate accordingly the cases of atherosclerotic aortic insufficiency from our series we find that only 6 of 41, or 14.6 per cent of cases of aortic insufficiency were associated with hypertension.

Only 6 of 75, or 8 per cent of patients with both mitral stenosis and aortic insufficiency had an accompanying hypertension.

The blood pressure in aortic insufficiency is difficult to evaluate. Characteristically there is a drop in the diastolic pressure and a moderate elevation of the systolic pressure which rarely exceeds 170 mm. of mercury. Such changes are due to the mechanical factors induced by the valvular lesion itself, and are associated with a peripheral vasodilatation. Diastolic pressures over 90 mm. of mercury and systolic pressures over 170 or certainly over 200 mm. of mercury cannot be attributed to the altered dynamics caused by the valvular defect, but must be due to peripheral vasoconstriction, analogous to that in essential hypertension. This view is supported by the necropsy findings, for in the aortic cases, too, true hypertension was almost always associated with arteriolar disease in the kidney.

Conclusion. Hypertension, often of considerable degree, is a common complication of chronic valvular heart disease. It is most frequent in patients over forty years of age. In chronic heart disease it is found most often in patients with mitral stenosis, occurring in fully 50 per cent of those over forty years of age. It occurs in valvular disease of rheumatic, syphilitic, and athero-

sclerotic origin. It is suggested that granular kidneys found at autopsy in these patients are caused by arteriolosclerosis consequent on a long-standing hypertension. The frequency of hypertension in our series is too great to be accidental, but a satisfactory explanation of the frequent association has not as yet been found.

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THE TREATMENT OF PAROXYSMAL AURICULAR TACHYCARDIA.

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There are two phases to the treatment of paroxysmal tachycardia.* In the first place, the attacks themselves present an immediate problem in therapy of varying degree depending upon the duration of the attack, the rate of the heart during the paroxysm, and the basic condition of the heart before the attack. Generally, the condition is of no great importance as the attacks often last but a short time and the patient is just as well afterward as before. Occasionally very disastrous results ensue. Rarely, death occurs or thromboses develop producing paralysis, gangrene of a limb, and the like.[1] Much is known concerning the treatment of the attacks themselves. They generally can be ended by one or another of the following measures: having the patient hold a deep breath; causing the patient to gag or to vomit; compression of the carotid artery thereby irritating the vagus nerve; or by ocular pressure. Very recently the use of quinidin sulphate intravenously has been introduced as a means of arresting such attacks.[2] We have had occasion in two patients to inject 0.2 to 0.3 gm. of quinidin intravenously, where all the customary methods had failed, with immediate cessation of the paroxysms. In most cases, the attacks are easily controlled by one of the above measures. The other phase of the treatment of paroxysmal tachycardia is the prevention of recurring attacks. It is this feature of the problem that this paper mainly considers.

Although the treatment of the specific attacks themselves has been quite satisfactory, in most cases little has been known concerning the prevention of a return of these attacks. In our experience the constant oral administration of quinidin has not proved effective. Similar disappointing results were obtained by Parkinson and Nicholl.[3] It is the purpose of this paper to discuss a new treatment that has been of great value in rendering patients free from such recurrences.

It commonly happens that although each attack of paroxysmal tachycardia is not in itself serious, the fact that they recur unex-

* This discussion deals with attacks of tachycardia, auricular in origin, and not paroxysmal ventricular tachycardia, flutter or fibrillation.

pectedly and with great frequency renders the patient incapacitated or produces a state of constant apprehension. In some instances, the severity of the spells makes it most important to use all available means that might prevent their return. Because many of these patients associate their spells with nervous and indigestion symptoms, sedatives, gastrointestinal medication and changes in the diet are often advised. Generally, these measures have been useless.

It has been generally thought that digitalis has no value in paroxysmal tachycardia. In this connection Cohn[4] states that "giving drugs, including digitalis, is unavailing." He does mention his experience in 2 cases of paroxysmal tachycardia. Some of the details in 1 were given and here it seemed that the patient remained free from paroxysms for short times while he was under the influence of digitalis, but that the attacks returned later. Sprague and White[5] also had a favorable result with digitalis in treating 1 of 3 cases of auricular tachycardia. From the results in our cases described below, it would seem that digitalis given in full and continued doses is very effective and of great value even where other measures, including quinidin, had failed. In 1 case, digitalis had been given in small doses during a period of months but had no influence whatever. When full doses were used the attacks disappeared. The use of small and insufficient doses may explain the fact that digitalis has in the past been discredited as having any therapeutic value in the prevention of attacks. The reason that it has not been given in sufficient doses in the past probably can be explained by the fact that this condition is not commonly associated with signs of congestive heart failure and the physician, if he gives digitalis at all, is apt to do so with only little confidence of its value. Furthermore it will become apparent to him that the digitalis given had no particular effect on the specific attack for which he is instituting treatment.

Case Reports. CASE I.—Housewife, aged sixty-six years, entered the hospital November 2, 1925. Eight years ago she began to have attacks of severe palpitation lasting from ten minutes to two hours. Many of these attacks were associated with the loss of consciousness. They gradually became more frequent and more severe. Between the attacks of palpitation she enjoyed fair health, but because they were so distressing and occurred without warning, her activities were very limited. She could not visit her friends and enjoy the simple pleasures of life. The spells were feared so much so that she constantly had a nurse in attendance for a period of a few years. Physical examination was essentially negative throughout. A course of bromides was given without any effect. She was kept on 10 drops of tincture of digitalis three times a day for some months but the attacks persisted. Then quinidin sulphate, at first 0.2 gm. twice a day and later 0.3 gm. three times a day, was given but there was no diminution in the paroxysms.

When seen during one of her attacks, the heart rate was 240 at the apex and the rhythm was perfectly regular. The patient was in collapse, the pulse could not be felt and the blood-pressure reading could not be obtained. Vagal pressure failed to end the attack, although pressure over the left eyeball instantly slowed the heart rate to 68. The blood-pressure reading then was systolic, 100; diastolic, 60. Subsequently vagal pressure proved very effective in controlling attacks which kept recurring.

On May 21, 1923, the patient was completely digitalized, receiving 0.4 gm. of digitalis a day for four days, then decreasing amounts until she was receiving 0.1 gm. daily. The attacks completely disappeared for a period of fifteen months. It was advised to stop digitalis to see whether the attacks would recur. One week after the omission of the drug she had her first spell and then digitalis was started again. There were no further attacks. Since November 1925, digitalis has again been omitted. Now she had been free from attacks even despite the fact that no digitalis has been taken. This case illustrates very strikingly the great value of constant digitalization in preventing most distressing attacks of tachycardia and the ineffectiveness of small doses of the drug.

CASE II.—Housewife, aged forty-four years, was seen in consultation November 2, 1925. For thirty years, the patient has had repeated attacks of palpitation associated with choking sensation of the throat. These spells used to last several minutes to a few hours but have recently been more frequent and of longer duration. Three weeks before the patient was first seen (November, 1925) she had an attack lasting twelve hours, during which the heart rate was 200 and the pulse was imperceptible. One week ago the attack lasted twenty-four hours. The attack, during which she was seen by us, lasted thirty-two hours.

On examination the patient was found to be in collapse, the skin was pale and cold. The heart was regular, 202 to the minute. Blood pressure was: systolic, 96; diastolic, 92. There were moist rales in both bases of lungs. Repeated attempts to stop the attack by vagal and ocular pressure failed. Her condition was critical and it was thought advisable to try intravenous quinidin. The injection of quinidin sulphate was begun. Although it was planned to give 0.3 gm., when 0.2 had been given and while the needle was still in the vein, the attack suddenly ended. The remainder of drug was not injected. The heart rate fell to 88 and blood pressure was: systolic, 102; diastolic, 78. The entire appearance of the patient changed and she promptly recovered her strength.

The next day digitalis was started. Full doses were given up to complete digitalization and then 0.1 gm. daily. For four and a half months there were no attacks whatever. Because she occasionally complained of slight nausea and in order that we might

learn whether digitalis was still needed to prevent the attacks, the drug was discontinued. Twelve days after the omission of digitalis, the patient had a typical attack of tachycardia with a heart rate of 200, which lasted twelve hours. She has now been digitalized again and has remained free of attacks. This case also illustrates in a striking way the beneficial effect of proper digitalization in the prevention of attacks of paroxysmal tachycardia.

CASE III.—Hospital orderly, aged forty-four years, entered the hospital April 8, 1925, complaining of palpitation which began twenty-nine years ago. Up to the age of thirty-nine years he had about three attacks a year. Since then they have been more frequent and more severe. They would generally last from a few minutes to six hours. During recent months, attacks would come almost daily and as a result he had to quit work. Electrocardiographic tracings taken during one spell were typical of paroxysmal tachycardia. His past history was unimportant. Physical examination was negative. The heart showed no structural abnormalities.

He was started on digitalis therapy receiving 0.5 gm. the first day then 0.1 gm. three times a day for a week. The attacks ceased entirely and he was able to resume his work. The patient did not coöperate very intelligently. It was impossible for us to keep in close touch with the events, but after one year had elapsed we learned that the attacks had been recurring for some months. He had discontinued the digitalis for long periods of time, taking an occasional pill now and then. February 23, 1926, he was again seen and it was learned that the attacks had been coming daily for some weeks. He was then digitalized again and now for the past two months there have been no attacks whatever.

This case also illustrates the fact that with small and insufficient doses of digitalis attacks might recur while with full doses they can be entirely prevented.

CASE IV.—Housewife, aged fifty years, first seen in consultation April 26, 1922. Attacks of palpitation began ten years ago and for the last seven years there has been sugar in the urine. First the attacks occurred every six months, later every month, and recently every week or so. They generally lasted about twelve hours. Between spells, she was in fair health and was able to do her house work.

When first seen in an attack the heart rate was 190 and perfectly regular. Left vagal pressure instantly ended the attack and the rate became normal and slow. Examination was negative except for a well-marked glycosuria.

She was getting an appropriate diet for diabetes and was told to take 0.1 gm. quinidin sulphate three times a day. For three months there were no attacks but then they returned more frequently

than ever despite the quinidin. The dose was then increased to 0.3 gm. three times a day, but the attacks continued. Her daughter was taught how to end the attack by pressing over the carotid artery and with the increased confidence thereby obtained, all medication was omitted. She was not seen again until January, 1925. This time attacks were coming once or twice a week. She was now thoroughly digitalized and all attacks ceased for six months. Digitalis was then omitted on the patient's own volition and the attacks recurred as frequently as formerly. She has not taken digitalis again because the attacks are so readily controlled by vagal pressure.

Summary. Four cases are described in which there were recurrent attacks of paroxysmal tachycardia extending over many years. In two instances, constant administration of quinidin sulphate failed to prevent recurrences. Thorough and constant digitalization proved effective in rendering the patients entirely free from attacks. In each instance, when digitalis was omitted, the attacks recurred. This method of treatment can be of great value when the attacks of tachycardia are frequent and incapacitating.

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THE "DANGEROUS UNIVERSAL DONOR."

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The "Universal Donor" (First Landsteiner Blood Group) is so-called because of the absence, in the corpuscles, of all of the isoagglutinable substances. Such inagglutinable corpuscles can exist after tranfusion into a recipient of any other blood group.

The presence of isoagglutinins in the plasma of the universal donor has not contraindicated the transfusion of Group I blood into

recipients possessing agglutinable corpuscles because, as Levine and Mabee[1] have shown, the quantity of plasma that is commonly transfused (250 cc.) is usually capable of clumping only 500 cc. of agglutinable corpuscles; that is much less than the normal whole quantity of the recipient's corpuscles.

In the recent paper just referred to, Levine and Mabee reported the occurrence of a Group I blood, in which there was an unusually high agglutinating activity toward all Group II corpuscles. This high agglutinating power rendered the blood dangerous for transfusion into any of the Group II individuals.

The existence of the dangerous universal donor, described by Levine and Mabee, was detected with the use of the method of direct matching of bloods, devised by A. F. Coca[2] upon suggestions by James Ewing, and later modified upon suggestions by Levine and Mabee and by L. B. Drake. In carrying out this method in the course of a class demonstration, one of us (A. J. W.), a Group I individual, was found by the test to be incompatible as donor to F., who possesses Group II blood, microscopic examination of the mixture prescribed for the test showing that most of the corpuscles in the field were agglutinated. This latter circumstance indicated that the agglutinated corpuscles were those of F., who was acting as recipient, and that the incompatibility was due to the same abnormally high agglutinating power of the Group I serum that was first described by Levine and Mabee.

The test in its final form is carried out as follows: The materials required are a white blood cell counting pipette, a Hagedorn needle, glass slides and cover glasses, and normal saline solution. Three or four drops of blood are obtained from the finger of recipient and donor in serologic test tubes, and defibrinated by stirring with wooden applicators. The stem of the white blood cell counting pipette is filled with the normal saline solution up to the 0.5 mark, and the defibrinated blood of the recipient is drawn into the pipette until the upper level of the saline solution reaches the 1 mark. The blood and saline are expelled upon a spot near one end of the slide and mixed with the end of the pipette, care being taken to avoid the formation of air bubbles. After the pipette has been rinsed, a similar 50 per cent dilution of the donor's blood is made and placed on another glass slide. Two divisions of this diluted donor's blood are then thoroughly mixed with the whole of the diluted recipient's blood, and the mixture is covered with a clean $\frac{7}{8}$-inch square cover slip. The cover slip is moved slightly from time to time, until agglutination is observed, or until fifteen minutes have elapsed.

The test was repeated and the result was found to be the same. The possibility of an autoagglutination of F.'s corpuscles was excluded by the observation that the mixture of F.'s plasma and corpuscles presented no clumping until W.'s plasma was added.

A quantitative determination of this agglutinating power of

W.'s serum was carried out in the following manner: A fixed quantity of W.'s serum (0.05 cc.) was mixed in separate serum tubes with graded amounts of F.'s defibrinated blood, a 50 per cent suspension of the cells. After mixture and centrifugalization, the tube containing 0.05 cc. of W.'s serum and 0.25 cc. of the 50 per cent suspension of F.'s cells showed complete agglutination. The tubes containing 0.05 cc. and 1 cc. of F.'s cells showed, respectively, moderate and slight agglutination, while the tube containing 0.05 cc. of W.'s serum and 2 cc. of F.'s cells showed no agglutination.

TABLE I.

	Tube 1.	Tube 2.	Tube 3.	Tube 4.
W.'s serum	0.05	0.05	0.05	0.05
F.'s cells 1 to 2	0.25	0.5	1.0	2.0
Gross agglutination in test tube	++++	++	+	−

This test seemed to show that W.'s serum was capable of agglutinating the cells of F. of Group II, at the ratio of 1 to 10. The possibility that the agglutinating power of W.'s serum was specific for F.'s cells led to further tests. Blood was obtained from three students, in Group II, and three students in Group III. We acknowledge our indebtedness to Spiegel, Garofalo, Rothfuss, Myerson, Gryzwaecz, and Coyne.

In these tests, we have followed the method used by Levine and Mabee. A 1 to 4 suspension of the cells was made by mixing the whole defibrinated blood with an equal volume of normal saline solution. The serum of W. was diluted 1 to 40, and 1 to 400. One-tenth of a cubic centimeter of the cell suspension was put in each of five test tubes, in each test. To these tubes, W.'s serum was added as follows: 0.5, 0.2, 0.1, and 0.05 cc. of the 1 to 40 dilution, and 0.3 cc. of the 1 to 400 dilution. The contents were mixed well by shaking gently and centrifugalized for two minutes at high speed. After this treatment, it was easy to determine degrees of agglutination by noting the presence of clumps after the sediment had been cautiously resuspended by shaking, the tubes being held obliquely during the resuspension. The estimation was facilitated by comparison with a control tube containing only the fixed quantity of the cell suspension and 0.5 cc. of saline solution.

The results of these tests are shown in Table II.

TABLE II.

Cells 1 to 4.	Serum W. 0.5	0.2	0.1	0.05 of 1 to 40	0.3 of 1 to 400
II, S.	++++	+++	+	−	−
II, G.	+++	+	±		
II, R.	++++	+++	+		
III, M.	+	−	−	−	−
III, G.	+	−	−	−	−
III, C.	+	−	−	−	−

It is seen that all but one of the Group II cells were agglutinated slightly by 0.1 cc. of the 1 to 40 dilution of serum W. (a ratio of 1 part of serum to 10 parts of corpuscular sediment), whereas none of the Group III cells was agglutinated by less than 0.5 cc. of the 1 to 40 dilution of W.'s serum (a ratio of 1 part of corpuscles to 2 parts of corpuscular sediment). This latter ratio is normal for most Group I sera, as Levine and Mabee showed. Thus it is seen that the agglutinating power of W.'s serum is normal for Group III cells, and abnormally high only for Group II cells.

Levine and Mabee did not test Group III cells with the serum of their dangerous universal donor, and it is possible that, in that case, also, the concentration of the β agglutinin was normal.

The question suggested itself whether the abnormal agglutinating power of W.'s serum for Group II corpuscles could be due to an excessive amount of agglutinin α'. This question could not be investigated. It may be pointed out, however, that the excessive agglutinating power of the Mabee serum could not have been due to an excessive amount of this element, because the Group II cells of Levine lack the agglutinable element A'.

The observation here reported illustrates again the importance of the direct matching of the blood of recipient and donor previous to transfusion. It also provides further evidence of the reliability of the method of examination with which the incompatibility was detected.

Summary. 1. The finding of a second "dangerous universal donor" is reported.

2. The "dangerous" agglutinating power of "universal donor" W.'s serum is due to the presence of an excessive amount of the α agglutinin. This quality would be exhibited against Group II and Group IV corpuscles.

3. The agglutinating power of W.'s serum against Group III cells is normal.

4. With W. acting as donor to individuals of Group II or IV transfusion of the usual volume of 500 cc. would cause some agglutination in an individual having a red cell count of as many as 5,000,000 cells per cubic millimeter, and would certainly cause fatal agglutination in an individual with a red cell count of 2,500,000, or less.

5. The importance of the direct matching test of Coca, as now carried out in a ratio of 2 to 10 instead of 1 to 10, as formerly, is emphasized, and the value of direct matching prior to any transfusion, to check up possible errors in grouping, and to detect unusually high-titered serum in a Group I individual, who is offering himself for the first time as a "universal donor," is obvious.

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BLOOD TRANSFUSION: EARLY ATTEMPTS, PRESENT INDICATIONS AND A DESCRIPTION OF THE SYRINGE-CANNULA-WITH-STOPPER METHOD THAT REQUIRES NO ASSISTANT.

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Historical. From certain ancient Egyptian and Hebrew manuscripts it is apparent that the transfusion of blood was at least considered a possibility in very early times and perhaps was even attempted, for in an old Hebrew manuscript appears the following:[1] "Naam, leader of the armies of Ben-Adad, King of Syria, afflicted with leprosy, consulted physicians who in order to cure him drew out the blood from his veins and put in that of another." If, as seems possible, this Naam is the same individual referred to in the fifth chapter of Kings 11 as "Naaman, Captain of the host of the King of Syria" it would seem that the transfusion failed to cure him for it was not until he obeyed the admonition of Elisha to bathe in the River Jordan that "his flesh became again like unto the flesh of a little child and he was clean."

It has been stated that an attempt was made to prolong the life of the aged Pope Innocent VIII by a transfusion of blood in 1492. Others who have investigated this claim believe that the blood, taken from the three youths who were bled to death, was used as a draught rather than introduced by transfusion, as the drinking of blood was not uncommon at this time.

The first transfusion upon a human being that we have definite knowledge of appears to have been done in France by Jean Denys of Montpellier, physician to Louis XIV, July 15, 1667,[2] though ten years previously the Benedictine monk, dom Robert des Gabets, had performed transfusions on animals. Denys' patient, a youth of about fifteen "had for above two moneths bin tormented with a contumacious and violent fever, which obliged his Physitians to bleed him twenty times in order to asswage the excessive heat. . . . We took about three ounces (of the patient's blood) at five of the Clock in the morning," continues the interesting account in the *Philosophical Transactions* for July 11, 1667, "and at the same time we brought a Lamb, whose Carotis Artery we had prepar'd, out of which we immitted into the young man's Vein, about three times as much of its Arterial blood as he had emitted into the Dish." At ten o'clock, five hours after the transfusion, "he was minded to rise . . . and for the rest of the day he spent it with much more liveliness than ordinary, eat his Meals very well and shewed a clear and smiling countenance." As he had been bled twenty times before the transfusion it is perhaps not surprising that a later

note states that the patient "grows fat visibly, and in brief, is a subject of amazement to all those that know him, and dwell with him."

That the first transfusion should be performed in France was a keen disappointment to the group of English experimenters lead by Richard Lower who had been performing transfusions for some time on animals and were only waiting a suitable opportunity to transfuse a human being. Their pique is apparent in the following paragraph from the *Transactions of the Philosophers:*[2]

"We readily grant, They were the first, we know off, that actually thus improved the Experiment; but then they must give us leave to inform them of this Truth, that the philosophers in England had practised it long agoe upon Man, if they had not been so tender in hazarding the Life of Man (which they take so much pains for to preserve and relieve), nor so scrupulous to incurre the Penalties of the Law, which in England, is more strict and nice in case of this concernment, than those of many other Nations are." The English architect, Sir Christopher Wren, was very much interested in the possibilities of blood transfusion and it was in a large measure due to his interest and enthusiasm that Lower and his coworkers began their work on animals.

Bad results naturally followed the promiscuous injection of animal blood into human beings and these fatalities together with the assertion that those transfused from animals would develop horns, deterred the timid and those of gentle nature from availing themselves of this therapeutic measure. So it was that the procedure was abandoned for upward of a hundred years.

In England James Blundell, the obstetrician, reported a successful transfusion of a patient with human blood in 1824, using a special syringe he devised for this purpose. He should be remembered, perhaps most, for the accuracy of his prophecy made one hundred years ago: "Transfusion by the syringe is a very feasible and useful operation and after undergoing the usual ordeal of neglect, opposition and ridicule it will hereafter be admitted into general practice."

With the discovery of the agglutinins and isoagglutinins in the blood by Landsteiner in 1901 and of the four blood groups by Jansky in 1907 and three years later by Moss, all that remained to make the transfusion of blood a safe therapeutic measure was the discovery of some method for transferring the blood from donor to patient before clotting took place.

Methods. Search for the ideal method has been prosecuted as assiduously as Ponce de Leon's quest for the "Fountain of Youth," and the month that does not bring forth at least one new method is indeed a barren one.

So much partisan bias and intolerance has been exhibited by the advocates of various methods that one must scrutinize with care much that has been written, lest one accept as fact that which is in reality only an unsupported opinion.

The citrate method does not demand a high degree of skill or an elaborate apparatus, but chills are more apt to follow than when unmodified blood is used. These reactions are not due to the citrate, *per se,* if it is chemically pure and properly prepared, as has been claimed, but in large measure to the chilling and manipulation of the blood that obtains with this method and to the use of improperly cleaned apparatus. New light has been shed on the causation of chills by the citrate method by Doan's recent work.[23] He found that when a blood is leukotoxic it is "doubly destructive to the susceptible white cell when citrated." Doan's studies will be referred to again.

It is not generally known that certain brands of rubber tubing when new possess properties that cause severe reactions, unless the tubing is soaked in "normal" sodium hydroxid for several hours.

Siperstein and Sansby[3] have demonstrated that the intraperitoneal injection of citrated blood is a safe procedure and that the blood so injected rapidly enters the circulation. They recommend it in infants because of its simplicity.

Inasmuch as reactions frequently follow the citrate method, even when performed by those of experience, other methods that transfer the blood while it is still warm and without exposure to the air are gaining popularity. The multiple syringe-cannula (Lindeman) method supplies the patient with warm unmodified blood and is ideal when a skilled assistant is available; but the unskilled assistant that necessity not infrequently furnishes is apt to pull the cannula out of the vein before the desired amount of blood is obtained.

Several ingenious and satisfactory types of apparatus have been devised for pumping blood from donor to patient through rubber tubing. This continuity of communication between donor and patient sometimes proves an embarrassment, however, and occasionally may constitute a hazard, in that after the transfusion is begun, it cannot be interrupted for a few minutes if for any reason this is necessary, without danger of the blood clotting in the tubing.

This necessity to proceed once having started a transfusion is sometimes fraught with grave danger. For instance, a highly nervous patient complains of symptoms that are impossible of immediate evaluation. If a mistake has been made in blood matching, as sometimes happens even with the most careful, and the warning symptoms disregarded, a fatality may follow the further administration of blood. On the other hand, if after a few minutes pause, during which time the patient's attention is diverted, the symptoms abate, one may slowly inject a few cubic centimeters more and again wait a few moments to observe the effects. This is not possible with closed circuits. Finally, the more complicated the apparatus the more difficult it is to clean, and unclean apparatus plays a large part in posttransfusion reactions.

A modification of the Lindeman method that eliminates the need

of an assistant occurred to me about a year and a half ago. This is accomplished by the use of a stopper fastened to the cannula, that occludes the opening when not connected with a syringe. As first described,[4] the stopper was suspended from the guard of an Unger needle by a fine chain, but more recently a watch spring has been substituted for the chain which holds the stopper up out of the way while the syringe is connected with the cannula. A transverse eyelet on the ventral aspect of the cannula, $1\frac{3}{4}$ inches back from the end, allows fixation of the cannula to the skin by a straight 3-inch needle, thus insuring the cannula remaining in the vein. Transfusion by this method in the operating room, or at the bedside, is performed as follows: Donor and patient lie side by side as in the Unger method, about 3 feet apart, with their proximal arms resting on arm boards. A small table for syringes and needles is placed in front of the operator, between donor and patient. A larger table next to the smaller one holds three large basins; two for sterile water and one for saline for rinsing the syringes. On the further side of this table stands the nurse who attends to the syringes.

The needles (Unger with eyelet and stopper) are introduced in the usual manner. As the needle is withdrawn from the cannula, the thumb of the left hand momentarily covers the end of the cannula until the stopper is introduced. A 3-inch Keith intestinal needle is next passed through the skin opposite the eyelet, then through the eyelet and finally into the skin adjacent. The stopper is then removed from the donor's cannula, the opening occluded with the thumb until a 20-cc. Record syringe, containing about 5 cc. of normal saline, is attached to the cannula and 15 cc. of blood aspirated. The stopper is then replaced, the one occluding the recipient's cannula removed and the contents of the syringe very *slowly* injected and the stopper inserted. If after a wait of two minutes no symptoms of incompatibility occur, one rapidly fills with blood several 20 cc. Record syringes (usually five with a good donor) and inserts the stopper into the donor's cannula. The blood is then quickly injected. Larger syringes have not proved as satisfactory. The syringes are washed in sterile water and saline and the transfusion continued.

It sometimes happens with a nervous donor who is being used for the first time, that the blood pressure will fall so low as to make it impossible to fill quickly more than two or three syringes at a time. One takes what he can get at the moment, as the donor will have a further contribution by the time the transfusionist is ready for more. With a good donor, one can fill five syringes each time and 500 cc. can be given in six minutes.

When this method of transfusion was first used 2 or 3 cc. of normal saline was placed in each syringe before filling, but this was found unnecessary. If the syringes are properly made and thor-

oughly rinsed the blood will not clot and no trouble will be experienced with the piston sticking. One hundred transfusions have been performed by this method, followed in 7 cases by a chill. With 2

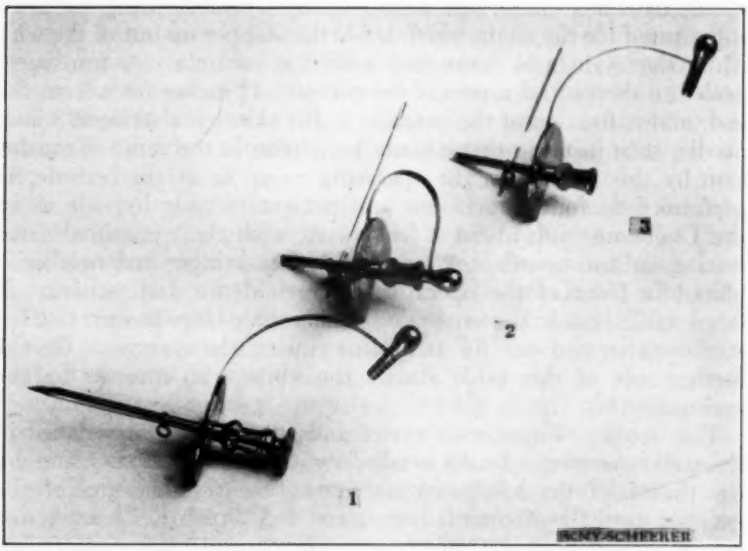

FIG. 1.—Unger needle with stopper and eyelet.

FIG. 2.—Cannula in the vein, thumb of left hand momentarily covering the opening as the stopper is grasped by the right hand preparatory to introduction.

exceptions, the chills all occurred in patients very ill with pernicious or aplastic anemia who had been transfused at least twice pre-

FIG. 3.—Introducing the needle that passes through skin, eyelet and again into skin thus holding the cannula in place. The stopper occludes the cannula.

FIG. 4.—Stopper removed and held up out of the way by the spring while the syringe is filled with blood.

NOTE.—Illustrations 2, 3 and 4 are from a motion picture taken by Dr. E. A. Wells.

viously and were perhaps in a refractory state. No serious reactions occurred.

Any amount of blood desired can be given by this method and

should occasion necessitate the transfusion can be interrupted for several minutes if the cannulæ are flushed with saline and the stoppers inserted, which is difficult or impossible with methods that connect donor and patient.

The small amount of apparatus, the absence of rubber tubing and valves, which are always difficult to clean, are additional advantages. If a patient with bacteremia (typhoid, syphilis, sepsis) is to be transfused, enough syringes should be employed so that no syringe will be used a second time.

That the operator, rather than the method, is often at fault has been shown by Lewisohn,[6] who found that reactions with both the citrate and Unger methods were three or four times more common when performed by junior interns than when done only by senior members of the staff. It may be that "anyone" *can* do a transfusion as the advertising matter of certain outfits states, but it seems pertinent to ask, *should* "anyone" do transfusions? The technique is not hard to acquire and the simple case with good veins, presents no difficulties but unless the tranfusionist is able to cope with the various conditions that may be met with, some of which are very trying, the success of the procedure and the life of the patient is seriously jeopardized.

I think it may be said that if one has the judgment to select only suitable cases, the "best method" is the one that each individual operator can perform most skillfully.

Selection of a Donor. The ideal donor is a robust individual with large veins, good morals and no "nerves." In practice, one has to use relatives and friends so frequently that the ideal is often not obtained. Syphilis, malaria and measles have been contracted through transfusions, but a careful history and examination of the donor, including a Wassermann test, will prevent such an occurrence.

No bad results to the donor follow the giving of blood. A study was made of a large group of professional donors employed every four or five weeks, over a period of years at the Mayo Clinic, and their general health was found to be excellent.[7] I have several times had donors tell me that they felt better after giving blood. In all cases where there is a possibility that transfusion will be needed—as in protracted typhoid, placenta previa, operations for sinus thrombosis, and so on—a compatible donor should be secured before the need occurs as the delay incident to testing a number of individuals may cost the patient his life.

By all odds the most important part of the transfusion is ascertaining that the donor's blood is compatible with the patient's. Time will not permit any detailed description of the various blood groups and the method of testing for compatibility. The donor should preferably be of the patient's blood group, but when a donor of the same group is not obtainable, blood from a Group I (Jansky) donor is usually safe, but inasmuch as there are several subgroups as well as the four main groups it must be demonstrated that the

patient's serum does not agglutinate the donor's cells. All blood grouping should be done in duplicate and it is always desirable to have the opinion of two individuals on the result of the agglutination test, the final reading of which should not be given before one hour. The operator should at least confirm, if not actually perform, his agglutination tests.

In considering the question of blood compatibility, attention has hitherto been focused upon the red cells, but Doan[23] has shown that certain individuals possess what might be termed "sensitive" white cells in that they are destroyed when they come in contact with the plasma of other individuals. This furnishes an explanation for the reactions that have occurred when the red cells matched perfectly. It is probably unnecessary to do a leukocyte compatibility test as a routine, but it is a precaution that might well be taken in a very feeble patient, where a reaction might be serious.

Reactions. The danger of using incompatible blood cannot be exaggerated as very severe reactions occur that are sometimes fatal. The warning symptoms are restlessness, flushing of the face, sweating, and pain in the lumbar region.

In the accounts of the early transfusions performed with animal blood one encounters reactions typical of incompatibility. On one of Denys' cases where "more than a pound" of calf's blood was used he states that the "pulse rose presently, and soon after we observed a plentiful sweat all over his face. His pulse varied extremely at this instant, and he complained of great pain in his Kidneys, and that he was not well in his stomack, and that he was ready to choak unless they gave him his liberty."

". . . He vomited store of Bacon and Fat he had eaten half an hour before. He found himself urged to Urine, and asked to go to stooll." (Later.) "He made a great glass full of Urine, of a colour as black, as if it had been mixed with the soot of Chimneys." Notwithstanding this severe reaction we are advised that in a few days the patient appeared to be greatly benefited. A mild state of excitement occasionally follows a transfusion. Mr. Heggenson, who devised an ingenious transfusion instrument in 1857,[2] tells of a certain patient, "exceedingly weakened from suckling twins for a long time," who became excited after a transfusion and "sang a hymn in a loud voice."

If, as has been said, the first 15 or 20 cc. of blood is introduced *very slowly* and the injection stopped if symptoms suggesting incompatibility appear, no bad results will follow. In an anesthetized or unconscious patient the warning symptoms will, of course, not be evident. I know of an instance where a very nervous patient was given, at her request, nitrous oxide just before the needle was introduced. She became conscious before the transfusion was completed and at once complained of severe pain in the back. The transfusion was immediately stopped but she died a few hours later.

Thermal reactions and severe chills are much more prone to occur in cases of primary anemia in which the degree of anemia is severe, and especially after several transfusions have been given. This heightened tendency to reaction may be due to the development by previous transfusions of some unknown and unrecognized antibody. Perhaps their plasma becomes strongly leukotoxic. There can be no question but that in some of these late cases of primary anemia it becomes increasingly more and more difficult to obtain compatible donors, and chills may occur irrespective of what method is employed, though they are less severe with unmodified blood.

An occasional case has been reported where a delayed reaction took place that suggested hemolysis, though the condition is not well understood. I have had one case where urinary suppression followed a transfusion, but whether it was due to the transfusion or was a manifestation of a delayed toxemia of pregnancy, I do not know. The patient was transfused because of a severe postpartem hemorrhage. During pregnancy she had only shown traces of albumin and the specimen before delivery was so reported. At the time of the transfusion performed about twelve hours after confinement, her color was distinctly yellow rather than pale, though the scleræ were clear. Seven hundred and fifty cubic centimeters were given by the syringe-stoppered cannula method without even the usual slight thermal reaction, but for several days following she passed only a few cubic centimeters of very bloody urine and the nonprotein nitrogen of the blood rose to 200 and the creatinin to 17. Notwithstanding these very high figures, she made a good recovery. The donor's and patient's blood was rematched after the transfusion and no agglutination took place.

Though anuria, in a few instances, has followed transfusion, it has also been relieved by the same procedure. Bowers and Trattner[8] obtained prompt diuresis, after the usual methods, including decapsulation, had failed, from repeated venesection and transfusions. Not long ago a colleague in this city secured an excellent result from transfusion in a case of urinary suppression.

A patient recently on my service with hemorrhagic nephritis was transfused because of a severe secondary anemia. For six weeks he had exhibited moderately high nonprotein-nitrogen and creatinin values, though on a low-protein diet. The nitrogen retention promptly disappeared following the transfusion, though there was no improvement in the phthalein output, which was only a trace.

Date.	Nonprotein nitrogen.	Creatinin.
June 5	80.0	5.3
June 11	75.0	6.6
June 21	71.0	5.4
July 23	66.3	8.1
(Transfusion, 420 cc.)		
July 26	27.5	1.6
July 28	29.2	1.5

The rationale of transfusion as a diuretic agent is suggested by Richards' experimental studies on glomerular function.[9] Studying the frog's kidney, he found that the number of visible glomeruli (visibility depending upon the presence of blood corpuscles within the capillaries) was increased by agents that increased renal circulation, among which was the injection of blood and that with the increase of interglomerular pressure, increased filtration takes place.

Indications for Transfusion. Transfusion is frequently indicated in the following conditions:

(*a*) *Hemorrhage.* Sudden large hemorrhage, as from gastric or duodenal ulcer; placenta previa, ectopic gestation, postpartum hemorrhage, typhoid fever and following tonsillectomy, mastoidectomy and sinus thrombosis operations.

Patients rarely bleed to death from the first large hemorrhage, but they sometimes do when the bleeding recurs, and I know of no sure way of determining whether a given case belongs to the majority who will not bleed again, or to the minority who will, though fatal hemorrhage is much less likely in youth than in middle age, with its vascular changes.

Whenever a patient has a hemorrhage, especially from the gastrointestinal tract, a compatible donor or donors, should at once be secured, so that there will be no delay if the bleeding recurs and a transfusion is decided upon.

When hemorrhage recurs following transfusion and there is a clear cut history of preprandial distress relieved by food or alkalines, one should seriously consider the advisability of attempting to locate and ligate the bleeding point either during a second transfusion or immediately thereafter. In the absence of the characteristic symptoms of duodenal ulcer, surgical intervention is apt to be unsatisfactory owing to the difficulty of locating the bleeding point, which may be in the esophagus rather than in the stomach.

The fear that a transfusion of moderate amount will start bleeding by raising the blood pressure is groundless as it has been shown that very low blood pressure is not materially raised, especially in the presence of large blood loss and the shortening of the coagulation time that results is greatly to be desired. Moreover, is it not likely that reparative processes will be initiated more quickly when the loss of red corpuscles is promptly made up?

(*b*) *Secondary Anemia.* Though the indications are not so apparent, or at least are not so generally recognized, it is to the cases of secondary anemia that transfusion has much to offer. These chronic secondary anemias are due to a variety of causes such as the slight but persistent bleeding from hemorrhoids, pyloric ulcer and uterine fibroids, and following protracted infections such as osteomyelitis, chronic empyema, abscess of the lung and ulcerative colitis. In cases of this sort a hemoglobin determination and erythrocyte count every five to seven days furnish a much better

index of the patient's resistance than can be gained by a series of leukocyte counts. Though cases of acute sepsis, including bacterial endocarditis are probably not benefited by transfusion, cases with chronic infection, if accompanied by anemia, may be greatly helped. Several transfusions of moderate amounts, about five days apart, are of great benefit, and Polak,[10] from his long experience with puerperal sepsis, considers this form of therapy greatly superior to mercurochrome and infinitely safer.

Nothing seems to stimulate the appetite like a blood transfusion. A patient with a severe anemia (primary) who had the usual distaste for food was recently transfused and she subsequently told me that the only thing she thought about on the way back to her room from the operating room was to wonder what she was going to have for dinner.

The slowing of the heart rate that usually takes place following a transfusion is also of distinct value.

In discussing a paper by Hess[11] on "Dehydration in Infants," in which, among other things, transfusion was advocated, Marriott[12] said, "The first thing to do with a malnourished infant is to give a transfusion to increase the tolerance for food." Leebron[13] found that twice as many of these moribund infants recovered if transfused.

(*c*) *Preparatory to Operation.* To convert a poor operative risk into a relatively good one. In this group are patients with secondary anemia who require a serious operation such as amputation, hysterectomy, splenectomy, nephrectomy, resection of stomach or rectum, mastoidectomy and patients with chronic jaundice.

Notwithstanding the fact that Baldwin[14] has shown that patients with a hemoglobin percentage of 20 or below may sometimes be successfully operated upon by a skillful surgeon, I agree with Lahey,[15] who in discussing the preoperative preparation of patients says: "No longer may one defend his position when operating on a poor-risk patient who has not had a blood transfusion previous to operation. It is almost criminal now for a busy operating surgeon or hospital not to have an available list of grouped and tested donors."

(*d*) *Shock.* It is now generally believed that the symptoms of shock are due to a universal capillary dilatation which results in so much of the blood remaining in the capillaries that the return flow to the heart is not adequate and the arterial blood pressure becomes very low. The individual bleeds into his capillaries, not into his veins as was formerly thought. As a result the tissues suffer from lack of oxygen, which in turn leads to still further dilation of the capillaries and in the more advanced stages, to increased permeability of the vessel walls, so that a loss of plasma occurs, thus aggravating the circulatory failure. Transfusion, if performed early, restores the circulation and corrects the serious oxygen lack to the tissues, but it is of much less value when shock has existed several hours. It, of course, should not be used to the exclusion of other

methods of recognized value. A transfusion performed just before or at the conclusion of an especially serious operation, prone to produce shock, such as resection of the rectum or splenectomy, materially diminishes the chances of its occurrence.

(*e*) *Severe Burns.* Many of these victims are children and the late Bruce Robertson[16] obtained very satisfactory results from transfusion in this group of patients which has a high mortality. In 10 cases where convulsions had taken place, an occurrence that ordinarily predicates a fatality, only 3 died from the burn toxemia. He preferred what he termed "exsanguinating transfusions"—bleeding and transfusing being performed simultaneously. He advocates giving an infant up to eighteen months 15 cc. per pound of body weight. Older children would receive correspondingly less.

Riehl[17] has recently reported a woman with severe burns covering more than 40 per cent of the body surface, whose life was apparently saved by blood transfusion. The rationale of transfusion in these cases is based on the fact that blood is concentrated in the capillaries in burns as in shock, and the administration of blood relieves the circulation and breaks the vicious circle, if the changes have not existed too long. A very high hemoglobin and red count are accordingly of ominous import, and a transfusion should be performed if no improvement follows the intravenous injection of hypertonic salt solution. The high mortality that obtains in infants with erysipelas lead Robertson to try blood transfusion, with very satisfactory results. The late Dr. John Howland, who had considerable experience with this same form of therapy, stated: "With all the hesitation that is necessary in the evaluation of therapeutic procedures, I feel that transfusion accomplishes a great deal."[18]

(*f*) *Blood diseases due presumably to some failure of the erythrogenetic function of the bone marrow, melena neonatorum, hemophilia, primary anemia.*

In melena neonatorum the administration of blood is life saving and the tendency to bleed does not persist in later years.

In hemophilia, though the result of transfusion may be spectacular, the condition is not cured. In view of the fact that the tendency to bleeding seems to diminish with later years, Ottenberg and Libman[19] suggest that a small amount of blood be given hemophiliacs every one to three months during the period of youth when injuries are so apt to occur and when the tendency to bleed is most marked.

There is no known treatment that will cure or materially modify the course of pernicious anemia (with the possible exception of large doses of hydrochloric acid and the high-protein (liver), low-fat diet recently suggested by Minot and Murphy[24]). Though the patient's destiny is seemingly irrevocable, transfusions ease the journey. The appetite improves; the annoying beating in the ears ceases for a time and there is a gain in strength. Remissions are probably

somewhat more frequent, but it has not yet been established that the duration of life is prolonged. In this group of cases moderate amounts (500 to 700 cc.) are safer than massive transfusions. It is, moreover, thought that very large transfusions (1000 cc. or more) inhibit the erythrogenetic system more than smaller amounts without affording it better nourishment. When cord symptoms with incontinence are present, transfusions are ill advised. Minot[20] believes that patients with primary anemia exhibiting an increased basal metabolic rate, providing that there is no marked evidence of impending marrow exhaustion, as evinced by large numbers of blasts, do better than when the rate is not elevated. Some member of the patient's family, if not the patient himself, should be told that the effect of transfusion in this disease is only temporary and that several will probably be required if the patient is to be kept reasonably comfortable. If it is decided to transfuse, the best results follow when it is not too long delayed, though transfusion during a crisis is not advisable.

The severe anemia that may accompany pregnancy, sometimes presenting a blood picture that cannot be distinguished from that of primary anemia, is greatly benefited by transfusion and Larrabee[21] has found that these patients remain well, thus differing from pernicious anemia with its frequent slumps.

Chronic idiopathic purpura is not permanently helped by transfusion but the results of splenectomy, preceded by transfusion, are spectacular, the bleeding often stopping before the operation is completed.

The secondary anemia which is so often present in the last stages of chronic leukemia and Hodgkin's disease, due to a general oozing of all mucous membranes, can sometimes be arrested and the patient's life prolonged for several months by transfusion. In acute leukemia, blood transfusion is of no value and perhaps harmful.

There may be some danger in transfusing a case with fresh vegetations on a heart valve. In one such case that I transfused because of an accompanying severe secondary anemia, thrombosis of the lateral sinus and death followed a few days later.

Bleeding, followed by transfusion, has been successful in cases of illuminating gas poisoning and should be used when the apparatus devised by Henderson[22] for the administration of oxygen and carbon dioxide in proper percentage is not available.

Summary. It is only in very recent years that the transfusion of blood has been made a relatively simple and reasonably safe procedure. Like all new measures whose indications and limitations are not generally understood, it is frequently recommended ill-advisedly and too often because the family or physician wants to "do something" when the situation is hopeless. It should not be looked upon as a last resort procedure.

Dangerous when not properly safeguarded, of little or no value in

acute infections unaccompanied by anemia, and of only temporary benefit in certain blood dyscrasias, transfusion is the most successful means of treating hemorrhage and shock and the grave secondary anemia of prolonged illness. In debilitated patients its preoperative use may be life saving.

The most desirable feature of the multiple-syringe-cannula-with-stopper method herein described is the fact that warm unmodified blood that has not been exposed to the air and has come in contact with a minimum amount of foreign material can be administered without an assistant.

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SERIAL HOURLY LEUKOCYTE COUNTS IN TERTIAN MALARIA.

As Observed in Malaria-treated General Paralytics.

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It has long been known that the parenteral introduction of various protein substances into the animal organism is almost invariably followed at a brief interval by a definite and often

well-marked leukopenia, which is not infrequently succeeded in turn by a leukocytosis of varying degree. Among the earliest observations of this sort seems to have been that of Albertoni,[1] who noted in the experimental animal a reduction in the number of leukocytes consequent upon the injection of a solution of pancreatin in glycerin, glycerin alone producing no such change. Shortly afterward the pupils of Alexander Schmidt in Dorpat made a similar observation in the case of a watery filtrate from macerated muscle tissue (Jauche[2]), of fibrin ferment,[3] and of peptone,[3] and they remarked in addition the presence of a leukocytosis at the end of twenty-four hours after the intravenous injection of these substances. A decade later, Roemer[4] reported a marked leukopenia, but no subsequent leukocytosis, to take place within a few hours of the subcutaneous injection of various bacteria in 10 per cent aqueous suspension, the subcutaneous and intravenous injection of filtrates of these suspensions, and the subcutaneous injection of living cultures of Bacillus pyocyaneus and other organisms. In the same year, Rieder[5] published the results of experiments on dogs in which he obtained a leukopenia (3000 to 4000 per cubic millimeter) one to four hours after the injection of aqueous suspensions (1 to 2 cc.) of Bacillus pyocyaneus (intravenously) and of the bacillus of Friedländer and Staphylococcus pyogenes flavus (into the knee joint), noting also that this leukopenia was followed by a moderate leukocytosis (13,000 to 15,000) of several days' duration. During the next few years, a similar phenomenon in the human subject came to the attention of those who employed antidiphtheritic serum in the treatment of diphtheria, the majority of whom observed after the injection of the serum a leukopenia which gave way after hours or days to a leukocytosis, usually of slight degree.[6]

Within the present century, a large number of observations have been published which demonstrate the almost uniform occurrence of a mild to marked leukopenia within a few minutes to one or two hours of the injection of substances not normally present in the circulation, the leukopenia being often but not always followed, after an interval of one to several hours, by a leukocytosis of variable intensity and duration. The substances which have elicited this phenomenon have included organ extracts, such as spleen, bone marrow, and thymus;[7] native proteins, as the serum of various animals,[8] milk,[9] and white of egg;[10] suspensions of a number of bacteria, especially Bacillus typhosus, Bacillus coli, staphylococcus and streptococcus;[10, 11] peptone,[3, 10, 12] deutero-albumose, and other proteins and protein derivatives.[13]

Since the adoption within the past ten years of the socalled nonspecific foreign protein therapy of certain diseases—notably typhoid fever, infectious arthritis, and gonorrhea and its sequelæ—identical observations with respect to changes in the leukocyte count have been made with some frequency upon the human

subject. Holler,[14] for example, observed that the intravenous injection of typhoid vaccine in typhoid patients was quickly followed by a leukopenia which reached its maximum at the end of the chill that succeeded the injection; from this point the number of leukocytes gradually increased, so that at the end of some six or seven hours a polymorphonuclear leukocytosis was present. Jobling,[15] who treated 19 patients with intravenous injections of 0.25 cc. of a 1 per cent solution of secondary proteoses, reported that following the injection, the leukocytes were decreased in number (even to 2000 per cubic millimeter), this leukopenia being followed by a gradually developing leukocytosis which usually reached its maximum in from five to seven hours and then declined to a normal level within twenty-four to thirty hours. In the same year Cecil[16] reported on 40 cases of acute arthritis which he treated with typhoid vaccine in a dosage of 40 to 80 million bacilli; in these he noted "a slight fall in the leukocytes immediately after the injection, followed in a short time by a rapid rise" such that the average count one to two hours after the injection was (in 5 cases) 26,000 per cubic millimeter. Scully,[17] likewise employing typhoid vaccine, found the reduction in the leukocyte count to coincide more or less with the time of the chill; toward the end of the first hour after the injection he observed a gradual increase in the count to take place, which continued until the maximum level was reached, about six hours after the injection, with a gradual return to normal by the end of forty-eight hours. The leukocytosis ranged from 13,600 to 77,200; a composite curve of 43 injections in 24 patients exhibited an initial fall from 14,200 to 5900 cells per cubic millimeter, with a subsequent average leukocytosois of 39,900. Culver[18] used killed gonococci in a dosage of 100 million. This produced, after twenty minutes to one hour, a chill lasting fifteen minutes to thirty minutes, with a subsequent rise of temperature to a maximum of 102.8° F. (39.3° C.) to 104.6° F. (40.3° C.) He says: "Usually there is a mild leukocytosis just before and during the first part of the chill, soon followed by a marked leukopenia which appears toward the end of the chill." A leukocyte count as low as 2000 per cubic millimeter was repeatedly observed. The leukopenia "is soon followed by a gradually developing leukocytosis which reaches its maximum in five to seven hours, remains moderately high for twenty-four to thirty hours, and returns to normal in about forty-eight hours." The maximum leukocytosis averaged (13 cases) 33,000 per cubic millimeter. Culver's experience with killed meningococci (100 million) and colon bacilli (25 million) was identical with the foregoing. Cowie and Calhoun[19] observed, following the intravenous injection of typhoid vaccine, an almost invariable decrease in the total leukocyte count, commonly but not always amounting to a distinct and often marked leukopenia, which occurred usually within two hours of the injection,

most frequently within the first hour. This leukopenia was always succeeded by a leukocytosis, of which the height was reached in from two to nine hours after the injection, most usually between four and seven hours. Associated with the injection of killed streptococci and of diphtheroid organisms, Gow[20] records only a very slight and much delayed leukopenia; but a colon bacillus vaccine produced a leukopenia four hours after the injection, at the end of the rigor, which was then succeeded by a leukocytosis of more than 20,000, although the latter did not reach its height until about the twentieth hour. When he employed Witte's peptone[21] (8 to 10 cc. of a 10 per cent solution), he found the maximum leukopenia to occur within three and a half minutes of the beginning of the injection, with a gradual increase in the count beginning immediately the fall was complete.

Two explanations have been advanced to account for the leukopenia following the injection of protein substances. Löwit,[22] Löwy and Richter,[23] and others, believed that an actual destruction of leukocytes—a leukolysis—took place. Bruce,[12] however, and in the same year Goldscheider and Jakob,[7] showed that no destruction of the leukocytes occurred but that they disappeared from the peripheral circulation owing to their accumulation in the capillaries of the internal organs, particularly the lungs; and recently Nagao[24] has carried out an extensive study demonstrating that in the case of the intravenous injection of nonhemolytic streptococci the outstanding features of the consequent cellular reaction are the accumulation of phagocytic polymorphonuclears in the capillaries of the lung, the liver and the spleen, and the great leukocytogenic activity of the marrow.[25]

Apart from the behavior of the leukocyte count, it is evident that there is a certain resemblance between the clinical phenomena which follow upon the intravenous injection of foreign proteins and those which characterize the febrile paroxysms of malaria; it is scarcely necessary to mention specifically the brief initial malaise, the chill, the sudden rise of temperature together with its often considerable height, the gradual defervesence frequently attended by profuse sweating, the duration of the total reaction, and the state of subjective health present in the intervals, which are common to both. Indeed, this resemblance has been commented upon by various workers: Holler[26] refers to it in passing, and Cowie and Calhoun[19] have discussed it at some length. It, therefore, appeared to the writer that it might be of some interest to discover whether an identity between the malarial paroxysm and the foreign protein reaction was also observable with respect to the behavior of the leukocyte count, especially since there is apparently no record of there having been carried out in the case of malaria the serial counts which have demonstrated in the other instance the changes in this respect which protein injections characteristically call forth.

On the other hand, statements of a qualitative character are not lacking regarding the blood picture typical of malaria. Böhm,[27] for example, states that at the beginning of the fever the leukocyte count rises to a more or less normal value—6000, 7000, or at most 8000, but with the further progress of the fever the count falls to 4000, 3000, even 2000 per cubic millimeter. Ross and Thompson[28] note the marked leukopenia which may characterize the pyrexial period and add that as the fever diminishes the total leukocyte curve rises, so that a week later it exceeds the normal and may even reach 20,000. More specifically, Kelsch[29] found that from the first hours of the attack the leukocytes became reduced uninterruptedly to a number only a half or even a third of that existing previous to the attack; "this over, the number increases much more slowly than it decreased." Stephens and Christophers[30] expressed their findings in terms, not of the number of leukocytes per cubic millimeter, but of the ratio of leukocytes to erythrocytes $\left(\text{normal, } \frac{\text{W.B.C.}}{\text{R.B.C.}} = \frac{1}{500}\right)$. They observed that some days before the attack, and before parasites appeared in the blood, a leukopenia was present $\left(\frac{\text{W.B.C.}}{\text{R.B.C.}} = \frac{1}{1000}\right)$; that during the shivering attack and the height of the pyrexia the condition changed to one of leukocytosis $\left(\text{so that } \frac{\text{W.B.C.}}{\text{R.B.C.}} = \frac{1}{300}, \frac{1}{200}, \text{ or even } \frac{1}{90}\right)$; and that this leukocytosis might not last long, but was followed by a marked leukopenia which was at its maximum before the onset of the next attack. Billet[31] has even plotted the leukocyte curve against the temperature curve, the counts having been made apparently at intervals of two or more hours; his chart shows a maximum leukopenia of $\frac{\text{W.B.C.}}{\text{R.B.C.}} = \frac{1}{1200}$ to $\frac{1}{1000}$ (about 3500 to 4000 per cubic millimeter) reached at the apex of the temperature curve, followed by a leukocytosis of $\frac{\text{W.B.C.}}{\text{R.B.C.}} = \frac{1}{400}$ to $\frac{1}{250}$ (about 10,000 to 16,000 per cubic millimeter) attained at the time the temperature has fallen to normal.

We would here report upon a series of hourly (and sometimes half-hourly) leukocyte counts which were carried out in the course of thirty-five malarial paroxysms occurring in 10 patients with general paralysis. In making the counts every precaution to secure accuracy was observed; at least twelve large squares, and often the entire ruled field, of a counting chamber 0.2 mm. deep were included in the count, so that ordinarily at least 800 cells were counted; blood was usually obtained from the finger, and the third or fourth drop utilized, in order to avoid all but the slightest pressure.

A definite reduction in the leukocyte count was observed in connection with thirty out of thirty-three attacks of "chills and fever." It was often not possible to obtain a count prior to the actual onset of the paroxysm, but only after the temperature had

already begun to rise; in fact, in ten instances, the reading on which the presence of a leukopenia was adjudged was the first reading made during the paroxysm in question, but in each case this count was 6000 per cubic millimeter or less. In the remaining instances, several counts of higher value had previously been obtained, and the count on which the presence of a leukopenia was established thus represented approximately the maximum reduction in the number of leukocytes per cubic millimeter which took place in the course of the given febrile seizure. It was found that this maximum reduction invariably took place during the latter part of the ascent of the temperature curve, often coinciding in point of time with the very apex of the latter; the diminution in the number of leukocytes thus had its onset at about the time of the chill, but reached its maximum some time after the chill (which usually lasted some twenty to thirty minutes) had passed off. The maximum degree of leukopenia reached, so far as this could be ascertained, ranged from 3500 to 6800 leukocytes per cubic millimeter; in three instances it was less than 4000, and in twelve less than 5000; the average minimum count for the thirty observations was 5100 (see table).

In 27 instances out of 35, the leukopenia was followed by a rapid and appreciable rise in the leukocyte count, amounting to a more or less definite leukocytosis (of 11,000 cells per cubic millimeter, or more) in 17 of these; in the remaining 10 the maximum count obtained remained below 11,000 (in 2, below 10,000), and could, therefore, be termed a leukocytosis only in the relative sense of representing a distinct increase, two-fold or greater, over the minimum value previously present. The maximum rise in the cell count, besides being extremely variable in degree, occurred at a somewhat variable period in relation to the temperature curve. More usually (in 10 instances) the leukocyte count reached its highest value one to two hours after the maximum temperature of the given paroxysm had been attained, though often (in 9 instances) only after three to four hours; but not infrequently (in 8 instances) the summit of the leukocyte curve coincided in point of time with that of the temperature curve, in which event an earlier occurrence of the maximum reduction in the cell count in relation to the rise of temperature preserved in general the usual interval of two to four hours between the occurrence of the maximum leukopenia and that of the maximum leukocytosis. The maximum degree of leukocytosis, so far as this was ascertained, ranged from 9100 to 27,100 cells per cubic millimeter; the average maximum count for the 27 observations was 13,600 (see table).

The curves plotted in Charts 1 and 2 are fairly representative of the relationship between the temperature and the leukocyte count in the individual malarial paroxysm as we have observed it in the majority of instances.

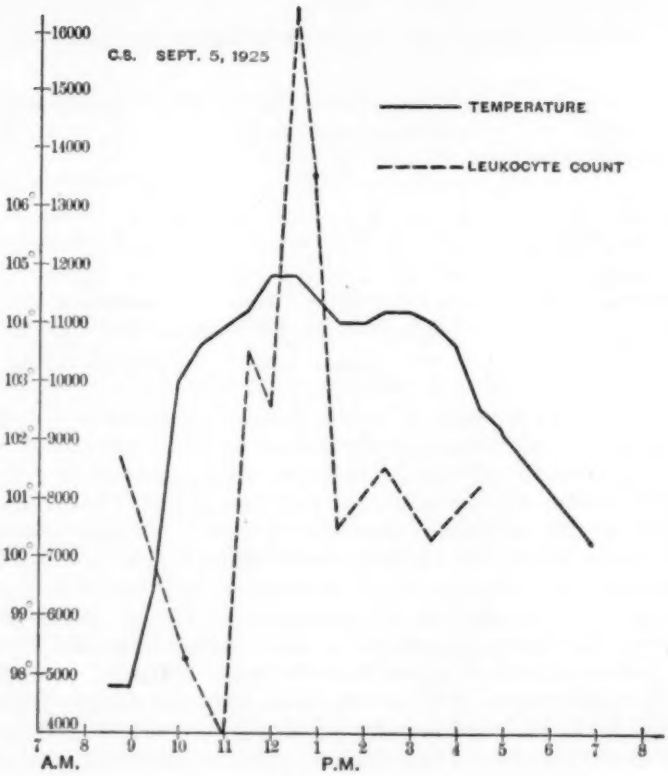

CHART I

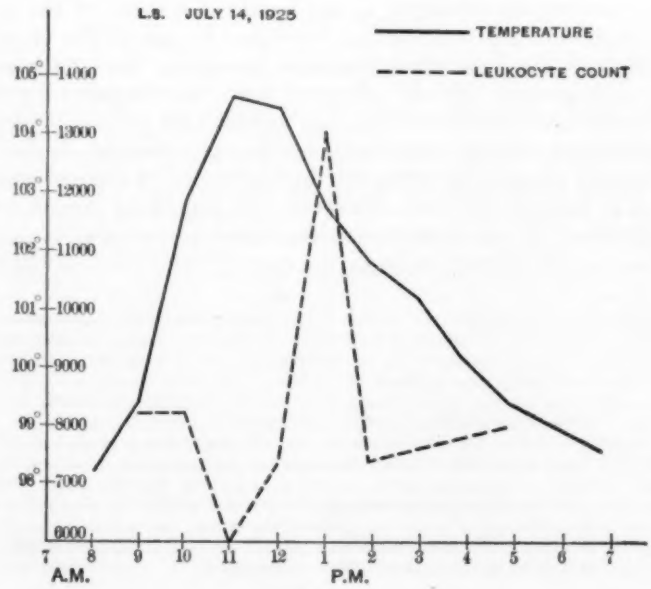

CHART II

TABLE.—BEHAVIOR OF THE LEUKOCYTE COUNT IN THIRTY-FIVE MALARIAL PAROXYSMS.

	Leukopenia.	Leukocytosis.
Present	30	27
Absent	3	8
No observation	2	0
Total	35	35
Maximum values	3500 to 7900 cells per cu.mm.	9100 to 27,100 cells per cu.mm.
Average value	5100 cells per cu.mm.	13,600 cells per cu.mm.

In sum, then, we have a certain amount of evidence that the leukocytes in the peripheral circulation undergo very much the same variations in number in the course of a paroxysm of tertian malaria as they do in connection with the sudden febrile attack induced by the parenteral injection of various foreign proteins. If the initial leukopenia be the primary phenomenon involved, the resemblance is somewhat closer perhaps, than if the subsequent leukocytosis is included in the comparison. For in the malarial paroxysm the latter appears to be less constant than the former and is often of minor degree; but the same statement not infrequently applies also, it is our impression, to the foreign protein reaction.* At any rate it seems justifiable to conclude that some event in the life cycle of the malarial parasite—an event undoubtedly connected with the recurrent rupture of the red blood cell and the liberation of the merozoites into the blood stream—is the more or less precise analogue, in the hands of Nature, of the artificial injection of a protein or like substance foreign to the circulation. But if the individual malarial paroxysm thus represents a recurrent protein "shock" identical with that induced by the intravenous injection of a vaccine, the source of the protein involved in the reaction remains uncertain: whether this protein consists of the liberated plasmodial segments themselves, or of some cleavage product of hemoglobin† also liberated into the blood stream with the rupture of the red blood corpuscle, cannot be stated at the present time; but the former seems on the face of it the more probable.‡

* A correlation between the occurrence of leukocytosis and therapeutic effect has been claimed by some[14] and disputed by others;[15] we can only state our failure to see any connection between the two in the few patients here reported, who have now been followed for more than a year subsequent to their course of malaria.

† For, while hemoglobin, which the malarial parasite destroys, is said to be nontoxic, one of its cleavage products, globin, is a protein of high toxicity.[32]

‡ It is perhaps well to remind the reader that the malaria here dealt with is the "inoculation" malaria employed in the treatment of general paralysis, which differs from the "natural" or mosquito-borne variety, *inter alia*, in that the sexual cycle of the parasite is suppressed, since the infection is transferred directly from patient to patient by intravenous injection of the blood of the donor; the paroxysms occur, in almost every instance, daily rather than on alternate days; and this type of malarial infection appears to be extremely susceptible to quinine.[33]

Summary. 1. It is a well-attested observation that the parenteral introduction of various protein substances into the organism is almost always followed at a brief interval by a definite leukopenia, which is not infrequently succeeded by a leukocytosis.

2. Since the febrile paroxysm of tertian malaria has a number of clinical features in common with the foreign protein reaction in the human subject, serial hourly cell counts were carried out during the attack of "chills and fever" to determine whether an identity between the two obtains with respect to the behavior of the leukocyte count as well.

3. A definite reduction in the number of leukocytes in the peripheral blood was observed in 30 out of 33 instances, with a subsequent leukocytosis of somewhat moderate degree in 27 out of 35.

4. The reduction had its onset at about the time of the chill, reaching its maximum during the latter part of the ascent of the temperature curve or at the apex of the latter; the maximum degree of leukocytosis usually followed by two to four hours the time of maximum leukopenia, near the summit of the temperature curve or more usually during its gradual descent.

5. The malarial paroxysm has thus, in this respect, the aspect of being a "natural" intravenous injection of foreign protein, in relatively massive dosage. The protein here responsible consists probably of the plasmodial segments (merozoites) discharged periodically and more or less simultaneously into the blood stream with the rupture of the containing red blood corpuscles.

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FOLLOW-UP OF ONE HUNDRED CASES OF GASTRODUODENAL ULCER TREATED BY MEDICAL MEANS.

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The fertile field of gastric and duodenal ulcer has been well worked over in past years. Since Courvoisier's masterful presentation less than one hundred years ago, symptomatology, pathology, etiology and definite courses and plans of treatment have been evolved. Roentgenography has added a more exact means of diagnosis and has furnished in addition, in many instances, a scientific method for controlling and evaluating the success or failure of a particular plan of therapy.

But in this field, as in analogous spheres of medical activity, a careful critical follow-up of the results of therapy, while attempted here and there on a small scale, has, relatively speaking, been insufficiently dealt with. The literary references on the end results of the conservative treatment of ulcer are few, widely scattered in various languages and literature; they bear various criticisms. In some the number of patients studied and followed have been too few; in others the period of time that has elapsed between the treatment and the follow-up period is too short. In still others, the original diagnosis is in question, particularly in those series which preceded the period in which duodenal ulcers were recognized as separate and apart from gastric ulcers.

The report about to be presented deals with 100 cases of gastroduodenal ulcer treated in the medical wards of Mount Sinai Hospital during the last four years, that is between the years 1922 to 1925 inclusive.

These 100 cases represent clinically evident and roentgenographically positive examples of gastric and duodenal ulceration. They have been investigated at this date, that is the *status presens* of these individuals is now known to us. In some instances, a small minority, we have had them under observation a greater part of the time since discharge from the wards; in most of the cases we have only recently learned the end result of their treatment to date, the patient in the intervening period having been entirely beyond our influence.

We do not, therefore, hold ourselves responsible for the present good or present bad state of the patients' ulcer welfare. The aim of our investigation is to determine in as large a group as possible

what is the eventual life history of ulcer cases; what is the effect of medical therapy on the course of the case; and after a lapse of time, what eventually happens to ulcer cases when conservatively handled.

The patients have practically all been seen and been studied by us within the last few months. A clinical report, physical examination and, most often, a radiographic study has been made. They are cases which underwent a modified Sippy diet, alkalies in moderate doses, bedrest and subsequent dietary caution upon leaving the hospital. Since the establishment of this follow-up bureau, about a year and a half ago, the opportunities for the continued observation of the hospital ward cases have been much improved. We now can follow the patient continuously from the day he leaves the medical wards to the present time. We keep him under observation, asking him to report and enforcing this request every three months.

It is recognized that 100 cases is a small group to report upon and that one to four years is far too short a period of follow-up observation. The fact that many of the cases have not been under our own continuous observation and treatment must also, to an extent, modify the responsibility for the end result after these years. This report must, therefore, be considered in the nature of a preliminary publication. The value of statistics of this kind enhances with each year; the series grows and the study-period lengthens. In due time and with continued effort a more exact and more valuable survey of this subject should result from these modest beginnings.

What are the *remote* results of the medical treatment of gastroduodenal ulcer after one to four years of observation and how do these results compare with the *immediate* effects of such therapy? From a perusal of Table I the following will be noted:

TABLE I.—IMMEDIATE AND REMOTE RESULTS OF MEDICAL TREATMENT OF ULCER.

Year of medical treatment.	No. of cases.	On discharge.		Recurrences, years.					Remote results.				
		Cured.	Unimproved.	½.	1.	2.	3.	4.	Cured.	Improved.	Unimproved.	Operations.	Deaths.
1922	22	18	4	1	4	3	3	1	6	5	2	7	(Perforations) 2 (1 death)
1923	17	14	3	1	3	1	6		7	4	1	4	1 death
1924	30	26	4	1	9	2			17	3	2	7	1 death
1925	32	28	4	4	4				21	7	3	1	(Carcinoma of lung) 0
Total	101	86	15	7	20	6	9	1	51	19	8	19	4
						43							

1. The immediate results upon discharge from the hospital are very good, namely 86 per cent are apparently cured, only 14 per cent remaining unimproved. These statistics agree well with those reported by Leube, Lenhartz and Nielsen for far larger series of cases and also agree in general with the published reports of most other observers.

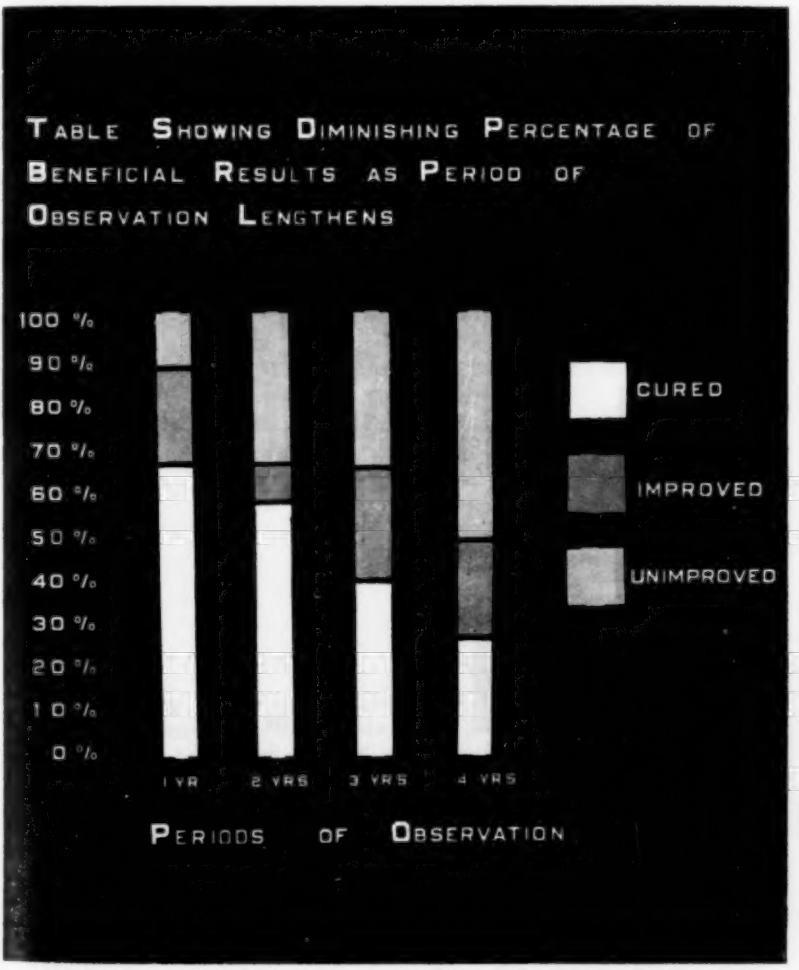

CHART I

2. Most of the recurrences of symptoms take place within the first year of discharge from the medical wards. The first six months are relatively immune from recurrences but within the first year 27 of these 86 supposedly cured cases (31.4 per cent) are already

showing recurring symptoms. With succeeding years new cases of recurrences are added to this doleful list but no longer at the same rate of progression. Within the period of our observation (one to four years) already 50 per cent of the apparently cured cases have relapsed. We are convinced of the important role that infections, particularly head colds, accessory sinus diseases, grippe and respiratory tract infections play in originating ulcer recurrences. A very large percentage of patients report recurrences of ulcer manifestations following one of the many seasonal grippe seizures. Diet seems to play, in this respect, much less of a role. We are not sure that excessive smoking is a dominant or even a contributory factor in originating recurrences. Nielsen's experience with early relapses is very similar to our own (see Chart II).

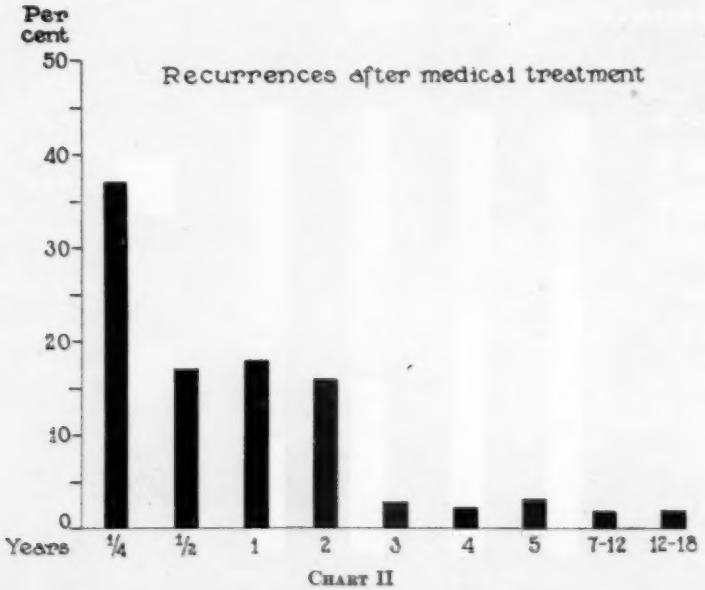

CHART II

3. The shorter the period of observation the better are the apparent results. The greatest number of cured (?) cases (21) are in the group followed for only one year. In the group observed for two years only 17 remained well; for three years only 7 cases; and those studied over a four-year period only 6 out of 22 cases can today be said to have remained free of recurrent symptoms.

4. A large number of cases have allowed themselves to be subjected to surgical operations for the relief of symptoms (19 out of 101 cases). Most of the individuals remain faithful to medical therapy for the first year but soon thereafter, corresponding with the greater number of recurrences, the percentage of those who

are forced to undergo radical treatment rapidly increases. In the group observed for four years, 7 out of 22 cases (31.8 per cent) have to date been operated upon for recurrent ulcer symptoms.

5. Few deaths occurred from ulcer under medical treatment. Only 3 cases of this series died while under conservative therapy—a remarkably low number. Of these 3 individuals 1 died of carcinoma of the lung arising in the bronchi; 1 died of pulmonary tuberculosis, undoubtedly aggravated by a severe and rebellious gastric ulcer, and 1 died of acute perforation of a duodenal ulcer. These two latter are directly attributable to the ulcer itself. If one excludes from the series the 19 cases operated upon, one notes in ulcer under conservative therapy a death rate of 2 out of 82 cases or 2.4 per cent. None of these cases died of subsequent hemorrhage, only one of perforation and none of malignant degeneration of an ulcer.

The appreciation of these data may be enhanced by a reiteration in table form of the salient points which have been made. Table II demonstrates the remote results of medical treatment in percentages.

TABLE II.—REMOTE RESULTS OF MEDICAL TREATMENT IN PERCENTAGES.

Year.	Cases.	Period of follow-up, years.	Cured, per cent.	Improved, per cent.	Unimproved, per cent.	Operations, per cent.	Perforations, per cent.	Deaths, per cent.
1922 . . .	22	4	27.3	22.7	9.1	31.8	9.1	4.5
1923 . . .	17	3	41.2	23.5	5.9	23.5	0.0	5.9
1924 . . .	30	2	56.6	10.0	6.6	23.3	0.0	3.3
1925 . . .	32	1	67.5	22.0	9.4	1.1	0.0	0.0

It will be noted that the percentage of cured cases (by cure is meant freedom of symptoms to date not necessarily permanent "cure") has already dropped from 86 per cent upon discharge to 67.5 per cent after one year of observation. This figure drops in the two-year class to 56.6 per cent, for three years to 41.2 per cent and after four years of follow-up one can claim only 22.7 per cent of apparently cured cases, following medical treatment. This per cent report does not include the results of the operated cases since, in all honesty, one must regard a surgical intervention in an ulcer case as a medical failure. The results of surgery upon ulcer are not germain to this paper and need not here be discussed.

The figures for "cure" after a term of years are made more reassuring and less depressing if one will include the percentages of those improved. It will be seen that if one wishes to do full justice to medical treatment one observes:

90 per cent of cured or improved after one year.
66 per cent of cured or improved after two years.
64.7 per cent of cured or improved after three years.
50 per cent of cured or improved after four years.

One may say that even after four years, medical treatment has cured or improved (symptomatically relieved) at least half of its cases.

What are the analogous results as culled from the literature? Most observers are more optimistic than we are, reporting similar but equally diminishing returns as the years of observation increase.

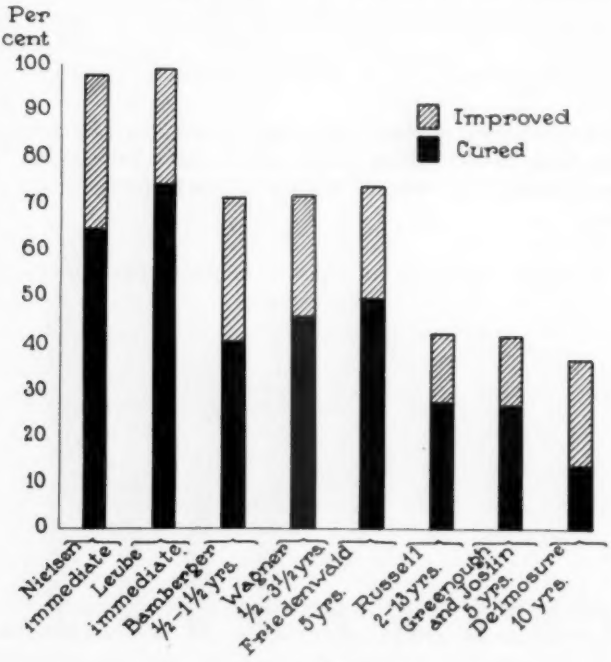

CHART III

Thus Friedenwald, after five years of a follow-up survey, reports 74 per cent of "cured or improved," Greenough and Joslin only 52 per cent for a similar group and period. After two to thirteen years of follow-up Russell reported 27.7 per cent cured and 15 per cent improved, and after a ten year follow-up Delmasure could find only 14 per cent cured and 23 per cent improved. These figures from the literature are surprising and far from reassuring for the ultimate outcome of medical treatment of ulcer of the stomach or duodenum.

Effect of Age of Patient Upon End Results. What effect has the age of the patient upon the end results of medical treatment?

A reference to Table III shows that the younger the patient during the course of therapy the better will be the ultimate result.

TABLE III.—INFLUENCE OF AGE OF PATIENT UPON OUTCOME OF MEDICAL TREATMENT.

Age of patient, years.	Total number of cases.	Immediate result.		Remote result.					
		Improved.	Unimproved.	Cured.	Per cent.	Improved.	Unimproved.	Operations.	Deaths.
10 to 20 .	1	1	0	1	100	0	0	0	0
20 to 30 .	11	8	3	8	72.7	0	1	2	0
30 to 40 .	30	22	8	13	43.3	4	5	8	0
40 to 50 .	33	31	2	17	51	8	3	5	0
50 to 60 .	17	16	1	9	53	3	2	2	1
60 to — .	11	7	4	6	54.5	1	1	2	1

The best results are seen in patients under thirty years of age, after which only approximately 50 per cent are eventually cured. All the deaths (2) occurred in individuals over fifty years of age. This again is a reassuring fact for the ulcer is a relatively common disease after thirty years and though only half the cases are cured the very low death rate is an interesting fact as affecting the longevity of the afflicted person.

Influence of Duration of Symptoms upon the Immediate and the Remote Results of Medical Treatment. It is of interest to note that the immediate results of medical therapy are good regardless of the duration of symptoms before the institution of the treatment. Patients who have complained for less than a half year show the best immediate results, over 95 per cent leaving the hospital well. On the other hand, those who have suffered for various periods of from one to two or up to ten or twenty years also show between 75 and 85 per cent of immediate recoveries.

Not so, however, for the late results. When followed over a course of one to four years a distinct difference becomes apparent. Those whose symptoms were less than half a year in duration still show over 70 per cent of cure after one to four years, but all those more chronic cases show less reassuring results. The long-suffering patient with symptoms continuous or intermittent for from one to twenty years can hope for only 37 to 47 per cent of cures after this period of follow-up.

Medical Results as Regards Duodenal versus Gastric Ulcer. There are many preconceived notions on this subject, some believing, particularly surgeons, that gastric ulcers never heal. And on the other hand, the remark that duodenal ulcers show less favorable results than gastric is a commonplace one. A critical analysis

of our follow-up does not show any marked difference between these two classes of cases.

The immediate results for both duodenal and gastric ulcers is about 85 per cent favorable. The remote results, after about

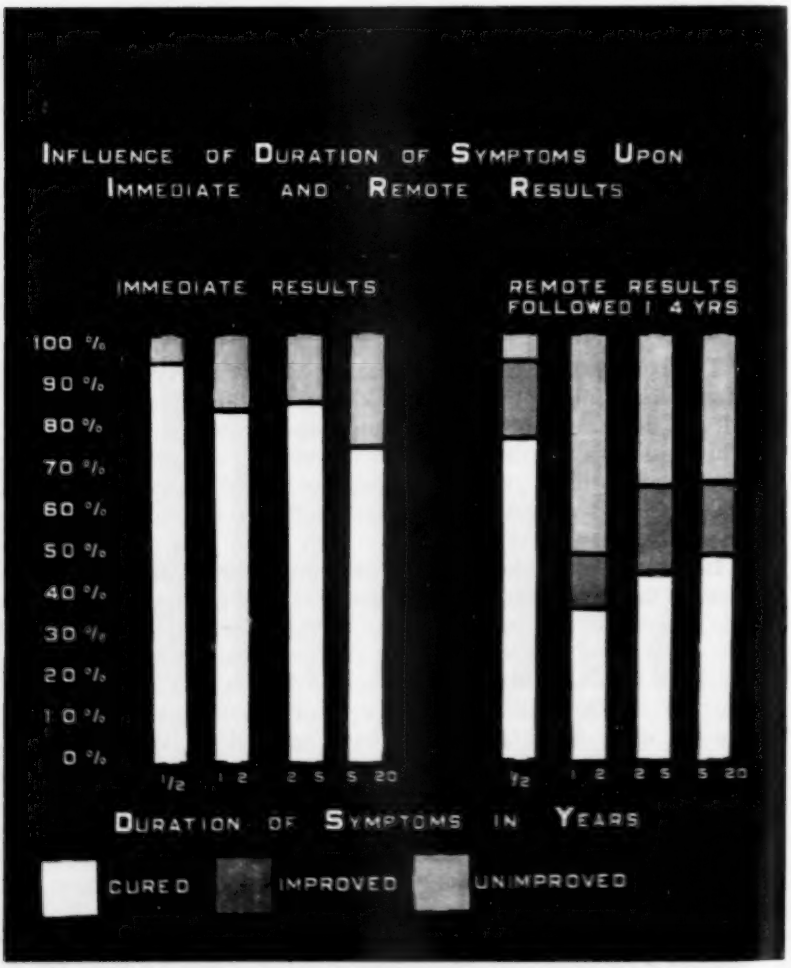

Chart IV

one to four years, indicate 52 per cent remote cure in the duodenal class and about 62 per cent satisfactory cure or freedom of symptoms in the gastric group. Such differences are not marked. And it will suffice to say that for statistical study both classes of cases may satisfactorily be grouped.

Discussion. We feel that the rather disappointing results of medical treatment as herein reported needs no apology from us. These patients were all cases originating in the lower working classes of the population with all that that implies, treated in the wards of a public institution and were then free to follow, or not to follow, the subsequent instructions we tried to impress upon them. We know that the original medical treatment received in the hospital was thorough and painstaking, as witness the large percentage of beneficial results upon discharge from immediate care. Had we been able to follow intimately and control all these patients in the succeeding years the results would have been proportionately better. Patients who exercise more discretion and conscientious

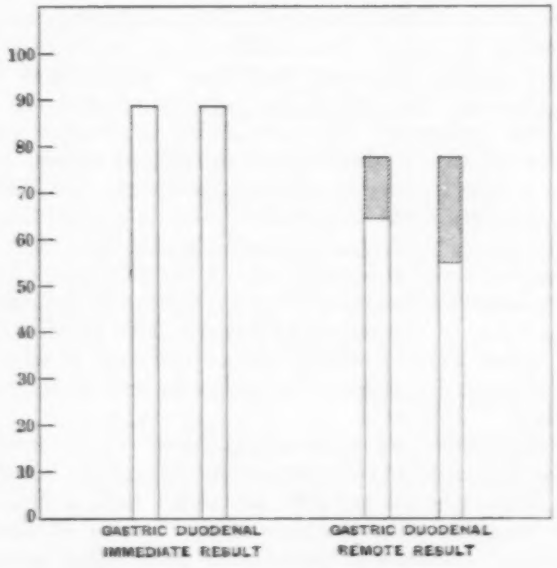

CHART V

care in the after treatment have the satisfaction of achieving a higher percentage of good results. While statistics from private practice are not at hand we feel that this latter class of patients gives eminently better results than those from the generally less educated class of workers, composed in addition mostly of breadwinners whose livelihood and the welfare of whose families depends entirely upon their continued daily effort without interruption. It was a repeated experience to find cases with recurrent gastric symptoms willing, but unable, to return for further observation because of the very stress and necessity of maintaining the upkeep of a family menage. To have achieved even so modest a percentage of good results is to some extent surprising and gratifying.

The higher percentage of cures reported by Friedenwald after five years follow-up is thus explained by the fact that most of his cases were drawn from his own private practice.

The lesson to be drawn from these statistics is the lesson of better and more persistent and more personally intimate treatment during the follow-up period of years.

When we have impressed upon our patient the fact that his malady is likely eventually to recur; that the continuance of his state of well-being upon leaving the hospital depends upon himself and the conscientiousness with which he unreservedly follows our instructions, then and then only can we hope for better statistical returns.

Follow-up of a Group of Penetrating Gastric Ulcers during a Course of Four Years. Finally we have attempted to study a series of penetrating ulcers of the lesser curvature of the stomach over a similar course of years. We observed 18 cases during these four years making frequent radiologic studies and keeping accurate notes on the size of the penetration and the clinical course of the symptoms. We have failed to observe malignant degeneration of any of these ulcers though, of course, the time period is too short to draw conclusions therefrom. In 11 of the 18 cases the penetration has disappeared; 5 of these cases showed the typical life cycle of ulcer, that is penetration has been observed and has disappeared under treatment; after a variable lapse of time the penetrating ulcer has reappeared at the same site and has again yielded favorably to conservative therapy. This peculiar behavior of gastric ulcers which probably has an analogue in what occurs in duodenal cases, is typical of the pathology and clinical course of this malady.

The remote results of penetrating ulcers, up to recent years regarded as incurable and as particularly dangerous, is very gratifying. A little over 60 per cent are today well, a figure which compares favorably with the percentage of cures of ulcers as a general group. Included in this class of penetrating lesions are a few cases of the acute type of penetrating ulcer, those in which symptoms have been complained of for a few weeks only. These cases give brilliant therapeutic results, both immediate and remote. Still more reassuring are the results in cases of chronic penetration in which the symptoms have endured for months, if not for years. Many of these individuals have required long courses of medical treatment lasting over one, two or three years during which time some form or modification of the Sippy diet has been practised. Under such repeated efforts, the penetration in even middle-aged and older individuals may be seen to become progressively smaller and to be accompanied by an amelioration of the symptoms and a continued gain in weight. Some of the most satisfactory results have been in men or women over fifty years of age.

These cases often lend themselves badly to surgical interference.

One of our cases was complicated by a hemiplegia, one by a moderately active pulmonary tuberculosis and many of them because of their age and the poor state of their general health would have constituted very poor surgical risks. We feel that a large penetrating lesion occurring in the middle-aged is a clear-cut indication for surgery because it is humanly impossible to differentiate the

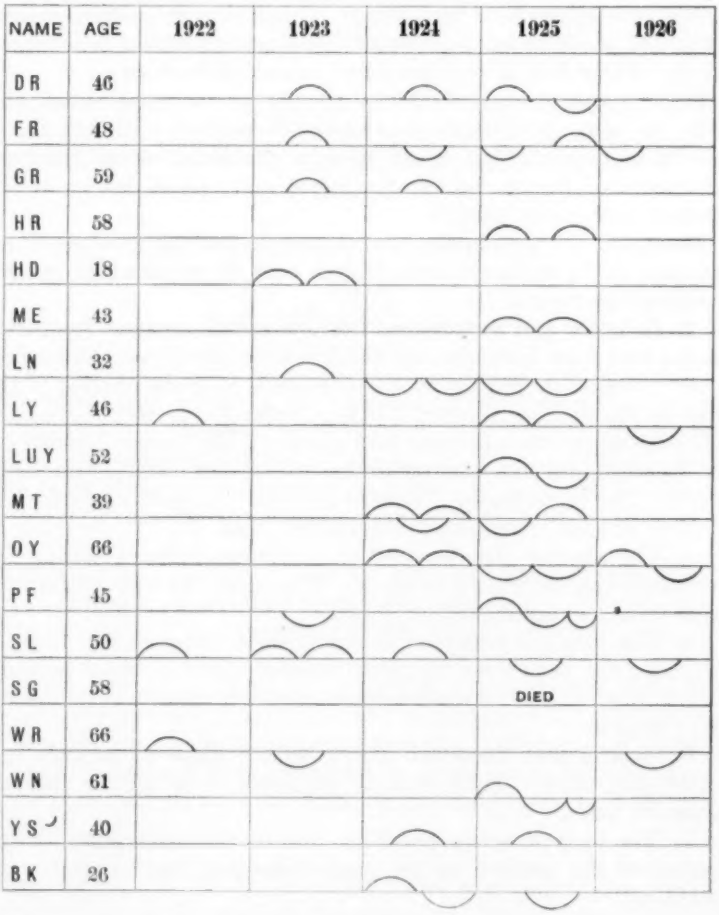

CHART VI

malignant from the nonmalignant cases. Yet these cases, most of which came under our observation only after several years of complaints, during which time they had outlived the fear and possibility of cancer, constitute an interesting group. They demonstrate the satisfactory outcome of persistent medical treatment upon the course of penetrating ulcers of the stomach. Only one

of these cases died and his life was terminated by an active pulmonary tuberculosis, the gastric ulcer itself remaining unhealed. It is of particular interest to note that no case of perforation occurred in this group.

Personally we do not feel that the presence of a penetration in itself is an immediate indication for operation. We feel that hemorrhage cases are entitled to careful medical treatment without serious fear of subsequent fatal hemorrhage. Similarly we consider it safe, if the fear of cancer has been or can be assuaged, to treat penetrating ulcers without fear of any imminent sudden perforation.

Both groups of cases should be treated by the same means and with the same perseverance as ulcers in general, with the likelihood that the end results will be no worse, if no better, than the demonstrated figures for uncomplicated and typical lesions of the stomach and duodenum.

Summary. 1. Immediate end results of medical treatment are satisfactory in approximately 84 per cent of all cases of gastroduodenal ulceration.

2. Relapses and recurrences take place with greatest frequency during first year; from then on the incidence of relapses diminishes.

3. A follow-up survey over four years is a demonstration of the "law of diminishing returns." The shorter the period of observation the better the apparent end results. The longer the survey extends the lower sinks the percentage of eventually and permanently cured. The percentages of cases which have submitted themselves to later surgical treatment is surprisingly high.

4. The shorter the duration of symptoms before treatment is instituted the better the outlook. The more chronic long-course cases show less optimistic end results.

5. The younger group of patients, those under thirty years of age, give far better results than those of ulcer in older persons. Still a very satisfactory percentage of ulcers heal even in the far older decades.

6. Gastric and duodenal ulcers behave alike as regards end results and cures. There is little difference to be seen in the two groups of cases.

7. The lack of better results is due to the inadequacy of the control of the patient in the years following the hospital ward treatment.

8. With improved personal control and a more close rapport between follow-up clinic and patient better statistical returns can be expected.

9. Penetrating ulcers of the stomach show very satisfactory end results after medical treatment. The life cycle of ulcer is here seen in its most typical form. The end results are good, over 60 per cent show cure. Perforation is uncommon. Penetration does not lead to perforation.

10. Acute penetrating ulcers heal very readily. Chronic penetrating ulcers may yield most satisfactory results under repeated and persistent medical efforts.

11. Malignant degeneration of ulcers has not been observed.

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PHYTOBEZOAR DIOSPYRI VIRGINIANÆ WITH REPORT OF A CASE.

By William B. Porter, M.D.,

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Phytobezoars found in the stomach of the human being are peculiarly rare. They consist of the skins, seeds and fibers of such fruits and vegetable matter as persimmons, prunes, salsify and celery, together with starch granules, especially those of the potato, fat globules, muscle fibers, elastic tissue, fatty acid crystals, and epithelial cells.

Before 1923 only 5 cases had been recorded, those of Schreiber,[1] Peple,[2] Outten,[3] King,[4] and Quain for Buckwill.[5] In that year Hart,[6] reported 8 cases coming under his observation. It is of special note that although these cases were observed in a section where the persimmon is not a very common fruit, in 6 of them the phytobezoar was composed of the seed and fibers of the persimmon.

The case here presented emphasizes the importance of careful differential diagnosis in chronic gastric diseases, the extreme rarity of the condition in no wise lessening its importance as a distinct clinical entity.

Case Report. J. C. H., a white male, aged thirty-five years, was admitted to the medical division of the Lewis-Gale Hospital, December 18, 1925. The patient complained of distressing gastric symptoms which had existed for thirteen months.

He stated that while hunting in November, 1924, he had eaten freely of persimmons between 4 and 5 P.M. He was positive he had not swallowed any of the seed. A few hours afterward he was seized with epigastric pain, nausea and vomiting, but at no time did the vomitus contain any part of the persimmons. For one

week he had acute gastro-intestinal symptoms, epigastric pain, nausea, vomiting and diarrhea. The diagnosis made by the family physician was ptomain poisoning.

Following the acute symptoms the patient had boring pain and burning in his stomach thirty minutes to two hours after meals. He stated that bicarbonate of soda gave complete relief for several hours and frequently a glass of milk between meals made him comfortable. There was never nocturnal gastric distress after the subsidence of the initial disturbance. There was nothing more of importance in the past or present history.

Physical Examination. The physical examination evidenced a man poorly nourished to the point of emaciation. The tongue was red and fissured but not furred. The cardiorespiratory apparatus was not unusual. The abdomen was scaphoid and there was no visible peristalsis or mass. In the epigastric area could be felt a hard, lightly sensitive mass about the size of a lemon. It did not move definitely with respiration, was at times quite distinct, while at others it was entirely absent from this area and could not be palpated. There were no other abnormal phenomena observed.

Laboratory Examination. Examination of the urine was negative. The blood count was: Hemoglobin, 68 per cent (Dare); red cell count, 3,320,000; white cell count, 8000; differential count, neutrophiles, 72; lymphocytes, 24; large mononclear, 2; eosinophile, 2. The blood Wasserman test was negative. Gastric analysis (Ewald test meal) was as follows:

Forty-five minutes: Free HCL, 50; total acidity, 80.
Sixty minutes: Free HCL, 44; total acidity, 76.
Seventy-five minutes: Free HCL, 36; total acidity, 58.

Gastrointestinal Roentgen ray Examination. Roentgen ray examination of gastrointestinal tract with barium meal showed a ptosis of the stomach, the lower border of the greater curvature extending, in the standing posture, about 3 inches below the crest of the ilium. Hyperperistalsis and hypermotility noted. An area of lessened density about the size of a lemon and having the appearance of a large air or gas bubble was seen in the stomach. This area was not coated with the barium mixture and was seen to change its position in manipulation of the stomach. Six-hour examination showed about one-fourth of the barium meal remaining in the stomach, surrounding but not coating over the area of lessened density described above.

Reëxamination of this patient three days later showed no change in the Roentgen ray findings. The area of lessened density was still present in the stomach, was freely movable during fluoroscopic examination, and was not coated over with the barium mixture. Six-hour examination again showed a retention of the barium meal in the stomach, enveloping the apparent air bubble, or area of lessened density.

FIG. 1.—Showing phytobezoars in the stomach, closely resembling an air bubble and composed of a mass of persimmons.

FIG. 2.—Showing phytobezoar partly enveloped in the barium mixture, six hours after its ingestion.

Centimeters

FIG. 3.—The phytobezoar removed. Weight, 59 gm.

We concluded that this area of lessened density noted at the two Roentgen ray examinations was due to a mass of foreign material in the stomach, and interpreted in the light of the clinical history, was most probably a ball or mass of persimmons, and operation was advised (Figs. 1 and 2).

Course in the Hospital. On December 24, 1925, the patient underwent an operation in which the stomach was exposed and a mass, irregular in shape and freely movable, was palpated in the stomach. This mass was removed through a vertical incision 2½ inches long.

The patient's postoperative course was uneventful and he left the hospital in three weeks, free from any gastric symptoms.

The mass removed (Fig. 3), weighed 59 gm. It was black, with irregular surface, having much the appearance of a lump of coke. A section of the specimen showed that it was composed of the fibers and skins of the persimmon, equally distributed, suggesting that it was formed promptly and no addition was afterward made to it from ingested food.

The patient was seen in May, 1926, and he remains free from all gastrointestinal symptoms.

Discussion. Manifestly, phytobezoar is extremely rare. In some of the largest clinics in America the condition has never been observed. (Personal communications.) It is highly probable, however, that many cases go unrecognized in the rural sections where the Roentgen ray is not available.

The history of the ingestion into an empty stomach of such foods as may cause a ball, followed by acute gastric symptoms lasting from a few hours to many days, in turn followed by subacute or chronic gastric symptoms which are not relieved by simple remedies, emphatically suggests the existence of phytobezoar. However, in the final diagnosis of this condition the clinical history should be augmented by the Roentgen ray examination.

In the bezoars, the Roentgen ray appearance of the gastric contour and silhouette is regular and smooth in outline. The area occupied by the mass gives the appearance of an air or gas bubble, or is faintly and diffusely shadowed with the barium mixture and should be freely movable during fluoroscopic examination.

The following should be differentiated: Benign tumors of the stomach, the pedunculated type forming polypi are especially prone to be confusing, but these should not be as freely movable or have as wide a range of motion as the bezoars. Gastric cancer, on the other hand, usually gives a definite filling defect and irregularity, the affected area of which is seen invading and involving the gastric wall and lumen. This defect is constant and fixed, with the absence of peristalsis in the involved area; there may be six-hour retention in the gastric cancer but in the bezoars there is always a six-hour stasis. Apparent filling defects, if plates alone are relied

upon, may be confusing as defects may result from faulty media in which the barium is not well mixed, excessive secretions in the stomach, gas in the colon, pressure of the stomach, against the spine, spasm, extrinsic abdominal tumors or many other allied conditions. However, with a careful fluoroscopic study, combined with serial plates, and a well taken clinical history, an accurate preoperative diagnosis should be made.

The salient question of the mechanism of the production of phytobezoars naturally excites one's interest. The persimmon contains 14.1 per cent of gum and 7 per cent pectin, which fact favors cohesion. A study of the reported cases and the case under discussion reveals the fact that the persimmons were ingested on an empty stomach. It is conceivable that the muscular action of the stomach, initiated by the ingestion of food, could easily mold and compress the substance into a mass. The high percentage of gum and pectin (plant jelly) in contact with moisture would form ideal conditions for cohesion of the cellulose fibers into a composite phytobezoar. The occurrence of acute gastritis with excessive muscular activity completes the process of molding so that the resulting alvine concretion remains intact, even after the gum and pectin have been removed by digestive process.

Conclusions. 1. Phytobezoars are rare, but they represent a distinct clinical entity and may be predicated in patients having chronic gastric symptoms, provided the onset has been ushered in with an acute gastrointestinal syndrome following the ingestion into an empty stomach of food containing a high percentage of gum and pectin.

2. A correct preoperative diagnosis can be made if the Roentgen ray findings are considered in conjunction with the clinical history.

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COLITIS AS A COMMON DISORDER OF DIGESTION.

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The severe forms of colitis associated with organic changes are well understood, easily recognized, and present no difficulty in diagnosis. These will not be discussed, except for passing references, in this paper. On the other hand, we should like to take up the milder cases of colonic irritability, particularly those in which the condition is still largely, if not entirely, functional in nature. These are frequently overlooked entirely, or are mistaken for atypical forms of other intraäbdominal conditions. It is to be borne in mind that colitis very frequently accompanies other gastrointestinal diseases, and may be quite overshadowed by a major condition. As the disturbed physiology due to the colonic malfunction is accountable for many disagreeable and troublesome symptoms, it is easy to understand why so many of these patients do not get along well on ordinary treatment.

The authors have long been impressed with the frequency with which simple colitis is encountered in the general run of cases, and with the relative infrequency with which it is recognized by the profession at large. Indeed, it is almost the exception to find a normally functioning colon among "chronic cases" of disordered digestion. Furthermore, the degree of discomfort present is often out of proportion to the physical findings and organic changes found in such persons. As a matter of fact, we find that 50 per cent or more of all patients complaining of digestive disorders show evidence of colitis, irrespective of what other conditions may be coexistent. The patient usually speaks of stomach trouble, and the physician is often misled by the patient's history, and treats him accordingly. The fact that the symptoms are brought about or aggravated by the intake of food makes for the impression that the condition is gastric in nature, while the stomach may be perfectly normal. The reason that the patient does not readily localize the seat of the disturbance is that the transverse colon and the adjoining flexures are close enough neighbors to make proper localization difficult, while the gastrocolic reflex accounts for the discomfort and pain, which is synchronous with or immediately follows the intake of food.

Etiology. What makes the simple forms of chronic colitis so prevalent? What are the etiologic factors which bring about a disordered colonic function? Some of these factors are well understood, while others are not sufficiently appreciated.

The various forms of constipation, atonic, spastic or rectal (dyschezia), tend eventually to result in colitis. If the injudicious use of cathartics is indulged in, the changes in the mucous membrane and deeper structures of the colon will come on sooner and be more pronounced. The recent fad of colonic irrigations, while these have their field of usefulness, is responsible for many cases of colitis. Improper diet, qualitative or quantitative, will often cause undue irritation of the gastrointestinal tract. Where gastric hypoacidity is present, even an ordinary diet may prove too great a burden for the colon to cope with. This is particularly marked in cases where short-circuiting operations on the stomach result in pronounced gastric hypermotility. Adhesions, from whatever cause, when they involve the colon producing a pericolitis, are often associated with colonic irritation. Intestinal dyspepsia, whether of the fermentative or putrefactive type, is always accompanied by a colitis. Finally, disturbances of the autonomic nervous control of intestinal function eventually terminate in a disordered bowel function. Where primary or superimposed infections play the major role, organic changes are usually present. These, however, represent the graver forms of the disease, and will not be discussed further.

Symptoms. The symptomatology is so protean in nature that errrors in diagnosis are very common When associated with other conditions, the symptoms of colitis are frequently overshadowed by the major pathology and overlooked altogether, but even when present alone, they are very often unrecognized. Colitis simulates appendicitis,[1] cholecystitis,[2] gastric and duodenal ulcer,[3] cancer, cardiac disease,[4] and others, depending on the segment of the colon which is most markedly involved. Thus, when the cecocolic tract is affected, the spasm will cause overdistention of the cecum, and pain in the right iliac fossa, and a symptomatology suggestive of appendicitis may be produced. When there is an excessive accumulation of gases in the hepatic flexure, the condition simulates a gall-bladder lesion to a nicety. Irritation of the transverse colon may be often mistaken for affection of the stomach or duodenum. Whenever there is discomfort in the epigastrium or in the umbilical region, the patient blames it on the stomach, and the physician only too often takes the cue from the patient. Only the most painstaking and careful history will put one on the right track.

Diagnosis. On physical examination, the patient usually shows tenderness over the various parts of the colon, and very often over the entire abdomen. Localized tenderness in the right iliac fossa or right hypochondrium is not uncommon and is very misleading.

Proctosigmoidoscopic examination is always useful. In the majority of cases, especially when the distal colon is involved, the direct inspection of the mucosa of the rectum and sigmoid clinches the diagnosis. Usually free mucus is seen lying in the gut.

The appearance of the mucous membrane depends on the stage of the disease and on the segment of the colon involved in the pathologic process. The changes are most marked when the distal colon is primarily affected. In early and mild (functional) cases, we find merely congestion of the mucosa. In the more severe and advanced (organic) cases, the pathology ranges from small punctate petechiæ and ulcerations to atrophy of the mucous membrane with large or small ulcers, or to the well-known polypoid appearance. Occasionally spasm is so marked that the introduction and passage of the instrument becomes quite difficult, the patient complaining of an undue amount of pain.

Test Meal. Examination of the gastric contents may prove to be helpful inasmuch as an achylia or marked hypochlorhydria when present is generally related to the associated colitis.

Feces. The stool examination is of utmost importance. In our opinion, the elaborate laboratory procedures described in the literature, although they have value in the hands of specialists, serve to discourage the more general recourse to this valuable aid in diagnosis. In the overwhelming majority of cases, a mere glance at the stool is sufficient for all practical purposes, yet it is just this simple inspection that is so often neglected. Given a stool which is mushy in appearance, contains an excess of mucus, gives evidence of fermentation by the presence of numerous small gas bubbles on the bottom and sides of the jar, is strongly acid in reaction, has a penetrating sour odor, and the rest of the examination is either superfluous or merely confirmatory. The outstanding feature in colitis, is the presence of mucus mixed with the stool, although Strauss[5] believes that even the failure to find mucus in the stool on ordinary examination does not necessarily mean that there is no colitis present, as the mucus produced in the proximal colon may be disintegrated by the time it is expelled with the feces. However, he believes that if cleansing enemata are employed, or sigmoidoscopic examination carefully done, mucus can usually be demonstrated.

The form and consistency of the stool also varies with the part of the colon involved in the pathologic process. The feces may be formed or semisolid, though in the majority of cases, there is an increase in the water content of the stool. The color depends ordinarily on the food ingested.

The microscopic findings vary in the different types of colitis. There is always an excess of mucus. With deficient gastric or pancreatic digestion, there is an abundance of meat fibers with or without striations. In fermentative dyspepsia, we often find incompletely digested starch granules or fungi which stain black with iodin. For more detailed methods of examination, reference may be had to books and articles on the subject.

The patient should always be put on a standard intestinal diet

(Schmidt) for at least three days preceding the examination of the stool, else the findings are not conclusive. The diet consists of a daily intake of 3 pints of milk, rolls and butter, 4 eggs, ¼ of a pound of chopped meat, strained oatmeal, potato soup, coffee or cocoa. It is important that the patient take all of the food prescribed in proportion to his weight, since with an insufficient intake, a moderate degree of digestive deficiency may easily remain undiscovered.

Roentgen Diagnosis. The roentgenologic aspect of the problem was studied by the senior author and will be elaborated more fully in a special communication.[1] It will be recalled that the filling and emptying of the colon takes place according to a definite time table. Normally, the cecum begins to fill four hours after the standard opaque meal. At six hours, the head of the barium column reaches the region of the hepatic flexure; the tail is still in the ileum. At nine hours, the head reaches the splenic flexure and the tail has cleared the terminal small intestine. At twenty-four hours, the bowels have moved once, and the left-sided shift has occurred, that is, the barium has cleared the proximal colon in whole or in part, and has become distributed throughout the distal colon. By forty-eight hours, the bowels have moved twice, and the colon is clear except for traces of the barium.

Any departure from the above schedule is abnormal. If the change is in the direction of stasis, a diagnosis of some variety of constipation is in order. If, on the other hand, the colonic transit is hastened, there exists a state of irritability, which is the essential motor expression of colitis. Colitis may therefore be diagnosed, or at least, suspected, from the following Roentgen findings:

1. At the "six-hour observation," the head of the barium column is beyond the splenic flexure.

2. At the "nine-hour observation," the head of the column is in the pelvic colon or rectum, with or without the passage of a stool containing barium.

3. At the "twenty-four-hour observation" the colon is empty.

In addition to the abnormalities of function, there are interesting changes in colonic form as revealed by a consideration of the sacculi or haustrations. Normally, these are deep cutting, evenly spaced, and evenly balanced, that is, the lumen is central, and the haustra on either side are equal in size, and symmetrical.

In colitis, there is either irregularity or complete absence of the haustrations, lending an atypical beaded, mottled or smooth appearance to the fecal colon, as the case may be.

Similarly suggestive is a scattered filling of the colon, or actual filling defect, provided of course, that obstructive new growth is excluded. This finding occurs characteristically in tuberculous colitis, producing the well-known Stierlin phenomenon (filling defect of the proximal colon). Increased gas content of the large intestine is likewise suggestive of colitis.

Finally, according to recent studies elsewhere reported, stasis in the terminal ileum is a strikingly constant finding in colitis. This may be diagnosed in one of two ways:

1. At the "six-hour observation" no barium has passed the ileocecal junction (relatively rare).
2. At the "nine-hour observation" barium is still present in the terminal ileum.

Prognosis.—The outlook for the absolute cure of colitis is often so uncertain that the prognosis must be guarded. However, it is not to be denied that some patients can be cured and many, if not most, can be relieved of their symptoms. In every case, however, the treatment must be exceedingly painstaking and long continued as the underlying autonomic instability is difficult to eradicate. Where grave organic changes have supervened, the task is that much harder. Furthermore, many cases still go unrecognized and are, therefore, either improperly or insufficiently treated.

Therapy. Before beginning any active interference, a complete and careful gastrointestinal survey is indispensable. Perhaps the first step in therapy is the absolute withdrawal of all forms of colonic abuse (cathartics, enemata, irrigations) so frequently indulged in by these patients.

The next step is to supply a bland and well-balanced diet. This is readily available in the form of the standard Schmidt diet, which may be concentrated as regards the number of feedings in the following manner:

Breakfast: One pint of milk, tea or cocoa prepared with milk; 1 soft-boiled egg; 1 buttered roll; 1 large plate of thick oatmeal gruel.

Dinner: One large plate of thick potato soup; ¼ of a pound of chopped or scraped beef, slightly browned in the pan.

Supper: Same as breakfast, with one or two additional rolls; also 1 additional egg.

In very irritable cases, it may be well to reduce the milk intake or to eliminate it altogether. Also, it may be necessary to split up the feedings and thus return to the original Schmidt plan of five meals a day. All cold foods and drinks are to be avoided.

If the above régime should prove too constipating, the best results will be obtained from appropriate doses of mineral oil, agar, or psyllium seeds.

Where on the other hand, the stools do not resume their normal form and consistency, the administration of an ounce or two of castor oil, repeated weekly if needed, helps to clear out old residues, mucus and bacteria. In other cases, sodium phosphate or other salts give better results, as some patients cannot stand even the mild irritating action of the ricinoleic acid. It is important that the salines be given in slightly hypertonic concentration and on an empty stomach, for when the salts are exhibited in too con-

centrated a form, the osmosis which takes place into the gastrointestinal lumen may prove sufficiently irritating to cause cramps or delayed action. The best results are obtained by giving the required dose in half a glass of water and following this immediately by a full glass of water on an empty stomach, preferably in the morning. No food is to be taken for at least thirty to forty minutes. There is usually a copious watery stool soon after the meal.

As the condition improves, other articles may be added, one by one, to the diet. The stools are to be carefully watched during this process, and, if they again become mushy, one must go back to the feeding which last gave a normal fecal output and try some other addition than that which proved harmful. Among the first articles to be added to the basic régime are well cooked chicken, rice, fish, and finely puréed starchy vegetables. Fermented milks or acidophilus milk are well borne by some patients. The last items to be added and with the greatest caution are the raw vegetables and fruits, and in general foods containing any mechanical or chemical irritants. Indeed such articles may never be tolerated by many individuals.

Medication is helpful, although there is no specific therapy applicable to all cases. Perhaps the inert bulky chemicals aid best in supplying the necessary roughage and mechanically removing mucus and bacteria by "adsorption." The ordinary barium sulphate as used for Roentgen ray diagnosis is admirable for this purpose. So is the bulky but lighter diatomaceous earth known as kaolin. Both of these powders must be taken in sufficiently large doses. It is our practise to give a tablespoonful of each stirred up in a cup of cocoa twice daily.

Other drugs may be used as occasion demands. The general sedatives (chloral and bromides together in small doses) are always useful to depress autonomic instability. If there is much pain codein may be ordered, though this is seldom necessary. For overcoming spasm atropin or belladonna in increasing doses is very helpful. We begin with as much as 10 to 15 drops of the tincture and increase the dose 1 drop daily until the symptoms disappear or the ocular accommodation is paralyzed. Where gastric anacidity exists, dilute hydrochloric acid is indicated, the dose being 5 to 20 drops in a glassful of water to be taken with meals. Conversely, if there is hyperacidity, a neutral antacid such as tribasic magnesium phosphate (Kantor[6]) seems to have value. The dose is one or more teaspoonfuls thrice daily.

In many cases, heliotherapy or the artificial actinotherapy seems helpful. Other patients respond favorably to warm moist compresses about the abdomen.

The organic colitides, especially those due to specific microorganisms and parasites require special forms of treatment which will not be discussed in this paper.

In all cases rest is important, and complete bed rest essential for the severe debilitating fluxes. Exposure of the patient to cold or wet is distinctly harmful. In general, the underlying neurosis should always receive intelligent attention and the treatment should include sensible advice as to hygiene, work, sleep and recreation.

Summary. 1. Simple (nonspecific, nonulcerative) colitis (colonic irritability) is a common disorder of digestion.

2. It is often overlooked by both patient and physician.

3. The diagnosis can be made: (*a*) Clinically; (*b*) by stool examination; (*c*) by the Roentgen ray.

4. The prognosis is guarded but improves in proportion to the precision of diagnosis and the persistence of treatment.

5. The therapy is outlined. It is primarily dietetic, but general hygienic measures, certain medicaments, hydrotherapy, and possibly actinotherapy are often of value.

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LIMITATIONS OF THE TUNING FORK IN THE DIAGNOSIS OF PULMONARY DISEASE.

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Percussion of the chest is based on its property as a resonator, auscultation of the thorax on its property as a conductor of sounds. Considering these two properties of the chest, can we utilize the tuning fork which plays such an important role in otology and in neurology for the detection of pathologic processes within the chest?

Let us review the laws of resonance. We recall from childhood the mysterious sounds heard in seashells. The secret whispered into the child's ears by the seashell is that the air is not silent; its inaudible vibrations are gathered to a loud chorus in the child's ear through the medium of the seashell.

If a vibrating tuning fork is placed on a solid piece of steel, wood

or wax held in the palm of the hand there will be no change in the intensity of its tone. If the pieces of steel, wood or wax are suspended on a thread, so that they are surrounded by air, and the experiment with the vibrating tuning fork is repeated, the same result will be noted. If, however, the same pieces of steel, wood or wax are placed on a table and the vibrating tuning fork is rested upon them a loud tone corresponding to the tone of the tuning fork will be produced.

The air-containing seashell and the table which forms the boundaries of an air column are resonators. A vibrating tuning fork set directly on the table will, of course, also produce a very loud amplification.

When the vibrating tuning fork is applied to the chest no amplification of the sound will be heard because the chest will not act sufficiently as a resonator.

Having shown that the chest is not a resonator for our purposes, let us consider the thorax as a conductor. The transmission of the tone produced by a tuning fork is heard very much louder through a dense medium than through one that is less dense. If a vibrating tuning fork whose tone is no longer audible is placed on an object, such as a piece of steel, and the bell of the stethoscope is applied to the object, a loud tone will be conducted to the ear. Similarly if a vibrating tuning fork is applied to the chest one can hear through a stethoscope a loud tone corresponding to the tone of the tuning fork. The chest will act as a conductor.

The problem at issue is: Will the thorax show any changes in its property as a conductor of sounds produced by a tuning fork when the organs of the chest have undergone a pathologic alteration?

Let us begin with cases showing on one side a hydropneumothorax and on the other side a normal lung. Place the vibrating tuning fork on the sternum and the stethoscope alternately on the posterior aspect of the right and left sides of the chest. Compare the intensity of the transmitted vibrations on the two sides as well as their duration. Two cases with hydropneumothorax, one right- and one left-sided, have been examined with this method. There was no difference in the character of the transmitted tone on the sound side and over the fluid on the diseased side.

Individuals with unilateral pulmonary lesions with and without evidence of cavitation, patients with bilateral lung lesions showing more extension of the involvement on one side and finally individuals with a pneumothorax without fluid were tested with the tuning forks, C, C^1, C^2, C^3 and C^4. A different technique was used. The vibrating tuning fork was placed on the midpoint of the patient's clavicle while the bell of the stethoscope rested on the supraspinous fossa of the same side. Then the intensity of the vibration transmitted from the left clavicle to the left supraspinous fossa was compared with the intensity of the vibration transmitted

from the right clavicle to the right supraspinous fossa, and the duration of the vibration heard on one side was compared with the duration of the vibration on the opposite side.

The vibration came through equally loud, and the duration of the vibrations remained unaltered on both sides in every individual, despite such marked tuberculous changes as a cavity which replaced in one of the tested individuals an entire lobe or as an accumulation of fluid occupying four costal interspaces.

Why did the chest containing fluid on one side act the same as a chest of a normal individual?

The following experiment may explain it. The examiner listened to a wooden box on which a vibrating tuning fork was applied, and compared the intensity and duration of the tone heard with a corresponding tone produced by a similar box, half filled with water. No decided variation was detected except for a negligible nasal quality of the tone emanating from the box with fluid. This suggests that the fluid in the chest cannot play any role in altering the conduction of the vibration of the tuning fork used in the described manner.

In further confirmation the following test was performed: (*a*) A rod was suspended by a cord and the lower end of the rod brought in contact with the floor of a wooden box; to one of the walls of the box a vibrating tuning fork was applied, and to the top of the rod a stethoscope; a loud tone was heard. (*b*) The same experiment was repeated with water in the box; while the lower end of the rod dipped into the water, not touching the floor of the box, a faint tone was heard which became very loud as soon as the lower end of the rod came in contact with the bottom of the box.

It may therefore be concluded that the water acted as a poor conductor as compared with the wood. From this it appears that the ribs act as the walls of the wooden box and that the vibrations of the tuning fork heard so distinctly on the chest of the tested individuals were not transmitted through the lungs, but through the ribs as a conducting medium. In placing the tuning fork in the costal interspaces the sound is conducted faintly.

A survey of the literature dealing with the physical examination of the chest reveals that though the tuning fork has been introduced for diagnostic purposes, a plausible explanation of the phenomena obtained has not been given. We meet assumptions and statements which have no ground, being contradictory to laws of conduction of vibrations in the chest wall.

Bass,[1] who introduced the term "phonometrie" in the year 1872, asserts that a vibrating tuning fork emits a louder sound when put over an air-containing organ of the body than over one which does not contain air. Bass writes: "By means of the phonometric method there can be obtained, as by percussion, not only information as to the normal position of organs and their outlines, as to

their changes within normal and pathologic limits, but also the degree of resistance which the examining part offers to the tuning fork by consecutive application." Bass makes no reference to the use of the stethoscope in his experiments.

Analyzing the findings of Maurice Mignon, as reported by M. Gley (1903[2] and 1904[3]), it is apparent that his procedure of studying the resonance does not exclude the factor of conduction. He applies the tuning fork to a costal interspace and compares by means of the stethoscope two points near to the tuning fork. If Maurice Mignon believes the increase of density in the lung tissue will give a better conduction, how can one differentiate whether a supposed change of the tone will be due to the space of a cavity (question of resonance according to Maurice Mignon) or to the dense wall surrounding the cavity? I will note also that the application of the tuning fork with equal pressure to two different points is practically impossible. A non-vibrating tuning fork placed with great care on the clavicle might produce a tone because of the slight impact; this tone can be heard over the corresponding supraspinous fossa. Another source of error is the movement of the chest wall during the respiratory phases. The tuning fork slides on the skin or with the skin.

R. N. Willson[4] writes (1905): "As the fork passes from normal tissue to a consolidated portion of the lung the pitch rises, and the note becomes much clearer; it may indeed become evident for the first time. If next it passes over a superficial cavity the note takes on a clear, sweet, musical character, which is never simulated by any other condition."

Schlesinger[5] expresses (1908) the belief that waves of sound move in a sagittal direction, for instance from the anterior surface of the thorax posteriorly. Utilizing this concept, he claims that when a tuning fork is applied to one surface of the thorax and the opposite surface is auscultated the intrathoracic organs can be outlined. Thus he is convinced that he can delimit the mesial border of the lung from the vertebral column, can outline some cardiac borders and he suspects that pleuritic effusions could be detected by phonometry. He hesitates, however, to utilize this method for the detection of small subpleural infiltrations.

Powell and Hartley,[6] discussing (1911) the value of combined ausculation and percussion point to a "new method based upon the belief that the vibrations of struck coins, or of a tuning fork placed upon the chest wall, are conducted over the chest partly through the parietes and partly through the underlying viscera; it is asserted that so soon as the limit of the viscus is overstepped, or we pass from one lobe of the lung to another, a corresponding hindrance to the passage of vibrations occurs, and the sound at once loses much of its intensity.

"We have tested this method on several occasions, but have not

been able to satisfy ourselves of its accuracy," sum up Powell and Hartley.

James Cautlie[7] writes (1914): "The principle involved in the use of the tuning-fork method is that when the stethoscope is placed over an organ, be it a solid one such as the liver, spleen, heart and so on, or a hollow organ such as the stomach or cecum, and the vibrating tuning fork is made to impinge on the surface of the body over one or the other of these organs, the note of the tuning fork manifests by its loudness the limits of the organ being examined, and the moment the limits are passed the note becomes faint, distant or is altogether inaudible."

Cautlie emphasizes that an effusion into the pleura is at once detected. Opp[8] partly verifies Cautlie and also claims that pleural effusions can be detected. He offers naïvely the following explanation: "I have been informed by a physicist that the vibrations of the tuning fork are heard through the stethoscope more distinct and louder when the stethoscope is placed over an organ, because that organ acts as a resonator."

The classical textbooks on physical diagnosis do not refer to any use of the tuning fork as an aid in diagnosis of pulmonary tuberculosis. Ernst Edens[9] briefly mentions the phonometric method, but gives no conclusions as to its value.

Summarizing the literature we observe that the thorax as a resonator has been overstressed, while its conducting mechanism has been overlooked.

Conclusions. 1. As a result of these experiments and observations on patients, we find that the presence of pathologic conditions of the lungs cannot be detected by the tuning fork:

2. This is due to the fact that the organs inclosed by the ribs are less conductive than the ribs.

3. This conductive power of the ribs suggests one possible explanation for the mode of the occasional transmission of rales or of cavernous breathing from a diseased lung to a normal one.

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FOCAL INFECTION IN ITS RELATION TO MEDICAL PROBLEMS: ITS USES AND ABUSES.*

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The most successful efforts in eradicating disease have followed the discovery of the cause.

Most diseases, the causes of which have been discovered, have been brought under control, while those still lacking a definite etiology are among the most difficult to prevent or cure, for example, cancer.

The discovery of the relation of localized chronic infections to many previously so-called constitutional diseases and degenerative processes is one of the recent great advances in medicine; one which has already improved the prognosis and reduced the incidence of such conditions as acute and chronic arthritis, acute endocarditis, chronic myocarditis, acute thyroiditis, acute nephritis, arteriosclerosis, retinitis, iritis, asthma, cholecystitis, gastric and duodenal ulcer, pancreatitis and many others.

I am entirely out of sympathy with those who believe that the removal of foci of infection in an effort to prevent, relieve and cure systemic disease is overdone. On the contrary, I am firmly convinced that the subject of the elimination of focal infection has not yet begun to receive the attention that its importance warrants.

To fail to advise the removal of an infected area, when its removal does not jeopardize the life or future health of the individual, implies either negligence or lack of knowledge and experience.

If we admit that a knowledge of the relation of focal infection to many diseases has greatly simplified our methods of approach, given us surer methods of treatment, has cut short many otherwise chronically progressive processes, and by accomplishing a cure by relatively simple yet decisive methods, has been the means of preventing chronic disease, curing apparently hopeless invalidism and of avoiding extensive surgery, then we must be willing to sacrifice the doubtful tooth, the chronically infected tonsil and the diseased sinus—such measures are the least of many evils. What harm if we do remove a number of teeth or a few tonsils without apparent benefit, if, by so doing, we are able to reduce the incidence of those diseases which now contribute to more than 25 per cent of adult human mortality.

The difficulties met in the elimination of focal infection and its consequences are many, and they are not all due to the refusal or objection by the patient to submit to the indicated treatment.

* Read before the Philadelphia County Medical Society, April 14, 1926.

My experience with many dentists has been disappointing. There is still a tendency among them to save at any price, obviously damaged teeth. Furthermore, they are prone to use as bridge abutments, without preliminary Roentgen ray examination, apparently sound teeth, the effect of which is to light up dormant infective processes and to provoke the development of apical and periapical infection.

The blindness of some rhinolaryngologists is beyond comprehension, and yet, there are a number who still refuse to admit that a history of recurrent tonsillar infection and the presence of chronically inflamed anterior pillars are evidences of chronic tonsillar infection, and who must see pus oozing from beneath the turbinates to agree that there is present accessory sinus infection.

It has been my experience when, by careful study and examination, I have located a focus of infection, to have my finding reversed by the consultant, and to eventually have my judgment vindicated by seeing chronic arthritis, thyroid hypertrophy, cardiac irritability, hypertension and so forth, relieved by a thorough exenteration and drainage.

What has been said of the accessory sinuses applies to the tonsillar situation. I have seen the laryngologist reluctantly remove tonsils which in his opinion were sound, and have had the satisfaction of seeing them exude pus during their removal.

Experience tells me that any tonsil, no matter what its apparent physical condition, when there is a definite history of previous acute disease, is a chronically infected tonsil and one which, in the presence of systemic disease of the varieties caused by a chronic focus of infection, should unhesitatingly be removed.

The value of the removal of foci of infection and the efficiency of this means of arresting and curing disease will depend upon the thoroughness with which the search for such foci is made, and the completeness of their eradication.

The more one considers the importance and necessity of systematic search for focal infection the more forcibly is brought home the fact that the periodic health examination is one of the best methods of conducting such a search. By it we are guarded against the dangerous tendency of accepting the first discovered focus of infection as the sole cause of distant pathology. Many of us have made this error because the exigencies of practice force us to seek the easiest way and to sacrifice thoroughness to haste.

I believe that a more general search for foci of infection as the starting point for diverse pathologic conditions will result in a far greater percentage of recoveries than has been had heretofore. So I urge you, who have not yet seen the closeness of this relation, to extend your methods of investigation and carefully consider the evidence found.

A serious mistake, and one to be studiously avoided, is that of

assuring the patient that the removal of a few diseased teeth, or the eradication of infected tonsils, will result in a certain and complete recovery. Such an attitude fails to take into consideration the possibility of multiple foci of infection. One should prognosticate cautiously, and insist on the removal of all foci of infection, eradicating the most obvious first, advancing promptly upon the next without great delay, until all discoverable foci have been removed.

Another source of failure, little thought of, but one sufficiently often met to demand consideration, is the fundamentally defective individual; that type who, at birth, is poorly equipped to run life's race by virtue of a fundamentally poor physique, who is continually in ill health and frequently incapacitated by conditions which in others would be trivial and easily overcome. My experience with this class leads me to be very doubtful of the end result, as not only does complete removal of all foci of infection often fail to accomplish the desired end, but even the primary foci themselves are most difficult to clear up. Sinuses fail to respond to proper surgery. Tooth after tooth develops periapical infection, and chronic intestinal stasis, which I include under the head of "focal infection," cannot be overcome by any known means.

I have mentioned the importance of a persistent and careful search. Such a study cannot be completed in an hour or two; the patient must be under careful observation and intensive study, sometimes in a hospital and every known method of examination employed to discover the presence of chronic infection in the teeth, tonsils, accessory sinuses, bronchial tree, gall bladder, appendix, prostate, tubes, ovaries and cervix, to which must be added, in the light of recent proctologic edict, chronic infection of the crypts in the anal region, called cryptitis.

Autogenous Bacterins in Focal Infection. I am a firm believer in the use of autogenous bacterins in the treatment of focal infection, particularly those made from the teeth or the tonsils. Their greatest value is in patients where the removal of a number of teeth is indicated, during which the danger of suddenly opening up blood and lymph channels to the infection is great. I have seen wholesale extraction of infected teeth precipitate an extensive acute multiple arthritis (Case I), but have never seen this occur when the following procedure was followed: Select one or, at most, two teeth showing definitely diseased apical areas; thoroughly scale and clean the teeth in this region, including those to be removed. Immediately upon extraction, the tooth still grasped in the forceps, is held over the mouth of a bouillon culture tube and the apex cut off with a rongeur so as to fall directly into the culture medium. The tooth socket is then entered with a small sterile swab, which is immediately rubbed lightly over a blood-agar plate or tube slant. When completed the autogenous bacterin is administered at from five to seven day intervals in ascending dosage, as governed by

the patient's reaction to it. After five or six doses have been given, multiple extraction can then be carried out with little danger of an acute exacerbation of the secondary foci of infection.

Autogenous bacterins are in many instances a great aid in the after treatment, during which they may be continued with benefit in maximum dosage for a long time.

The following seems to me a plausible explanation of their effect. When we remove a focus of infection we may stamp out the original conflagration, but we do not directly influence the secondary foci that have resulted from it. By using the bacterin we reach, through the blood stream, these secondary areas, and by raising the patient's immunity to the bacteria causing the original infection, favorably influence the disease processes which we desire to cure. Whether this is the true explanation or not, there is no doubt in my mind that more prompt results frequently follow their use than where they are omitted.

Case Abstracts.* The following cases illustrate some of the points which I have endeavored to emphasize. They are all cases treated in private practice and are of types commonly met. For purposes of brevity, much of the accumulated data regarding them have been suppressed; all were intensively studied by the usual clinical and laboratory methods.

The first case illustrates the danger of multiple extraction of teeth in one whose resistance to infection has become temporarily lowered, in whom wholesale extraction of teeth precipitated an acute attack of multiple arthritis.

CASE I.—R. R. M., aged thirty-six years, a clerk, was first seen in the spring of 1917. During the past five years he suffered several recurrent mild attacks of multiple, painful arthritis, involving, at various times, all the extremities. The diseased condition of his teeth had been noted, but Roentgen ray examination was refused, and the patient only appeared when he desired relief from the pain, which he could not accomplish by selfmedication. During the summer of 1917 he suddenly desired to have his teeth Roentgen rayed, following which 9, showing apical infection, were removed at one sitting. Within twenty-four hours he developed a chill followed by high fever, which ushered in the most serious attack of arthritis he had experienced. During the attack which confined him to bed for nine weeks he developed an acute cardiac condition, which nearly cost him his life.

* The following reports have been received since the preparation of this paper over six months ago:

CASE II.—Last report September 23, 1926; weight 220 pounds; no recurrence of arthritis.

CASE III.—Last seen September 21, 1926. On general diet; weight 140 pounds; considers himself in perfect health. Blood examination May 12, 1926, hemoglobin, 87 per cent; red blood cells, 94 per cent.

CASE IV.—Last seen September 24, 1926; weight 188 pounds. Condition excellent. Has had no thyroid medication during interim.

CASE V.—Last report September 23, 1926; no recurrence of original symptoms, no noticeable thyroid enlargement. Weight 124 pounds. Patient dieting to prevent too great an increase in weight. Feels perfectly well and continues her occupation as teacher.

He finally recovered after a period of restricted activity lasting many months. I last heard of him about three months ago, when he was in excellent health, never having had a recurrence of his arthritis.

The following case demonstrates the necessity of searching for, and the importance of removing, every discoverable chronic focus of infection. In this instance it was necessary to remove infected teeth, diseased tonsils and finally the gall bladder and appendix before the desired result was accomplished.

CASE II.—Mr. H. S., aged forty-eight years, a manufacturer, was first seen, July 10, 1923. He contracted syphilis nineteen years ago and has had frequent attacks of arthritis during the past ten years. Tonsillectomy was done in 1916 in an effort to relieve his arthritis, which began two years before. His last severe attack of arthritis was two years ago. The present attack began July 1 and involved the feet and sacroiliac region.

Examination. Wassermann test, negative; mouth in poor condition, containing a number of devitalized teeth. The old tonsil stumps were large and the anterior pillars injected. There was tenderness in the gall bladder region; no other important findings. Roentgen ray of patient's teeth showed five or more apical abscesses. He was advised to have the teeth removed, but refused.

The patient was next seen, March 31, 1924, on account of an acute alveolar abscess. Tonsils were reddened, swollen and the patient had fever. Extraction again refused.

On June 12, 1924, an acute digestive disturbance was accompanied by slight epigastric pain, anorexia and vomiting lasting two days.

On November 30, 1924, an acute attack of arthritis involved the right knee and both feet; it lasted three weeks, during which the patient had a tooth removed, from which an autogenous bacterin was made. After four injections, which gave little relief, four teeth were extracted on December 19, followed by temporary relief.

On December 30, 1924, both extremities, including the right hip joint, became involved. Between December 31, 1924, and March 6, 1925, the patient was partly relieved by sixteen intravenous injections of sodium salicylate and sodium iodid, each 15½ gr. per dose.

On January 26, 1925, tonsillectomy was followed by prompt relief, and the patient was comparatively comfortable for six weeks, when an acute exacerbation occurred, which involved all four extremities.

Further search for foci of infection suggested a gastrointestinal Roentgen ray. This showed a large gall bladder containing, at least, one large stone and a chronic appendix. Two days later the gall bladder and appendix were removed. Relief was prompt, but convalescence slow. There has been no recurrence of arthritis to date, almost fifteen months since the operation, and the general physical condition of the patient is much better than formerly.

The following is a case of duodenal ulcer which perforated, and was operated upon, in whom there later developed a pelvic abscess which required operation and drainage, to be followed in a short time by a massive hemorrhage, producing a grave secondary anemia, presumably from an ulcer on the margin of the gastrojejunostomy site. Extraction of four diseased teeth followed appropriate treatment, rapidly restored the blood and returned the patient to normal activity in a comparatively short time. In the

light of experience, the original ulcer, the pelvic infection, the marginal ulcer and the hemorrhage might all have been prevented had the patient been subjected to thorough physical examination prior to the development of the duodenal ulcer.

CASE III.—Mr. C. E., aged thirty-five years, married, clerk, was admitted to Misericordia Hospital, December 18, 1924, with a diagnosis of perforated gastric ulcer. He was immediately operated upon by Dr. George P. Muller. A duodenal ulcer was found and a gastrojejunostomy performed. At the time of operation his hemoglobin was 70 per cent and the red blood cells 83 per cent. Five days later the hemoglobin was 70 per cent and the red blood cells 81 per cent. Postoperative recovery was uneventful. Patient discharged, cured, January 15, 1925.

He was readmitted, March 17, 1925, on account of general soreness over the entire abdomen following a chill two days before. Examination showed moderate distention, rigidity in the lower half and exaggerated peristalsis. By rectal examination, there was some tenderness in the pelvis and a suggestion of a mass. He was under observation for twelve days when a right rectus incision revealed free pus. The wound was closed with drainage. Culture showed hemolytic streptococci, and the blood hemoglobin 80 per cent; red blood cells, 75 per cent. Discharged, cured, on April 26.

The patient was readmitted, December 7, 1925, with a diagnosis of anemia following gastric hemorrhage. At this time there was upper abdominal pain, great weakness, vomiting and tarry stools. The blood showed hemoglobin, 60 per cent; red blood cells, 58 per cent. Ten days later hemoglobin, 63 per cent; red blood cells, 65 per cent; there was present anisocytosis, polychromatophilia and many microcytes and macrocytes. He was transfused the same day (500 cc. of citrated blood) without benefit, as two days later the hemoglobin was 43 per cent and the red blood cells 54 per cent. At this point the patient was transferred to the Medical Department and came under my observation, when the most important finding was five apical abscesses. These teeth were extracted by Dr. William McKinley, on December 23, 1925.

A Sippy diet and symptomatic treatment was begun. This included iron and arsenic by mouth and cacodylate of iron and strychnin by intramuscular injection. Between December 19, 1925, and April 5, 1926, the patient received forty injections. His blood picture on December 21, 1925, was hemoglobin, 43 per cent; red blood cells, 54 per cent. At the close of the treatment the hemoglobin was 62 per cent and the red blood cells 85 per cent. During this time he increased in weight from 125 to 145 pounds; at the completion of treatment the patient was working eight hours a day, was and still is in good health.

The next case is one of hypothyroidism with hypertrophy of the thyroid. It illustrates the failure of simple thyroid medication when the disease is secondary to focal infection. In this patient the foci were multiple, and it was necessary to progressively eliminate them all before the desired recovery was accomplished.

CASE IV.—Mrs. E. M., aged fifty-four years, was first seen, October 17, 1924.

History Summary. During the past three years the patient experienced increasing fulness and a sense of constriction in the neck, gradually interfering with speech, accompanied by dyspnea and orthopnea, dizziness with a subjective sensation of falling forward, pain behind the right eye, palpitation and numbness in hands. It was noticed that the skin was very dry and that she did not perspire easily but was very sensitive to

exposure to cold and was always chilly. The hair was coarse and dry. She was very constipated. She was unable to attend to her household duties on account of extreme physical weakness, and was rapidly becoming deaf.

The patient had been treated sometime before coming under my care by rest and thyroid medication without material improvement.

Examination. Weight, 207 pounds; blood pressure, 160/90; pulse, 112, intermittent. Bilateral soft thyroid enlargement, causing visible deformity of neck; mentality dull. Speech at times almost unintelligible. Deep tendon reflexes were very sluggish. Skin was dry, rough and scaly. The nose showed a deflected septum with bilateral ethmoiditis. The tonsils were enlarged and chronically infected; anterior pillars injected.

Neurologic Examination. No evidence of disease of brain or cord.

Ocular Examination. Beginning neuroretinitis, otherwise negative.

Roentgen ray Examination. Lungs negative; heart hypertrophied (myocardial degeneration); sclerosis of arch of aorta; substernal shadow; probably substernal goiter. Accessory sinuses; right ethmoiditis, probably involving sphenoid, otherwise negative.

Electrocardiogram. Left ventricular preponderance.

Laboratory Examination. Basal metabolic rate, +2; urea nitrogen, 13.2; sugar, 134; nonprotein nitrogen, 56.4; creatinin, 1.5; hemoglobin, 70 per cent; red blood cells, 70 per cent; white blood cells, 3350.

General Summary. On November 18, 1924, the patient had a tonsillectomy by Dr. C. T. McCarthy in the Misericordia Hospital.

From the day of operation the patient's general condition improved. Her mentality cleared, speech became normal, hearing improved and she was not annoyed by cold as formerly. By December 18 she weighed 181 pounds (loss of 26 pounds). Her blood pressure was 130/80; pulse, 80, regular. Two months later Dr. McCarthy performed a submucous resection and cleaned out the right ethmoid region, following which the patient experienced further relief. At this time thyroid medication was begun and continued until June 15. This was given in increasing doses, up to 12 gr. of the Burroughs Wellcome product per day. Her weight was 178 pounds; pulse, 76, regular. She had none of her previous symptoms, although she still tired easily, and was short of breath on exertion. The skin was of normal texture; she perspired freely; mentally and physically she was normal.

She was again seen on November 2, 1925, when her weight was 176 pounds; blood pressure, 120/90; pulse, 72, regular; hemoglobin, 100 per cent; red blood cells, 91 per cent. Last seen, April 13, at which time there had been no recurrence of her previous symptoms.

The following case is one of acute hyperthyroidism with beginning exophthalmos. This is interesting in comparison with the preceding, as it illustrates the fact that focal infection may unfavorably influence thyroid activity in either direction.

CASE V.—Miss E. G., a student, single, aged nineteen years, was first seen, December 21, 1923. There was no history of this condition in any other member of the family, and in the patient it developed quite rapidly, following a sore throat several weeks before. It was noticed that her eyes had a frightened expression, she was short of breath, complained of being chilly with sore joints, had precordial pain, difficulty in swallowing, had lost weight, was constipated and could not continue her school work on account of nervousness.

Upon examination her pulse was 136, the eyes distinctly staring and von Graefe's sign absent. There was fine tremor of the hands and tongue.

Deep tendon reflexes were exaggerated and she was extremely restless. The tonsils which were supposed to have been removed twelve years before were large, flat and inflamed. The anterior pillars were injected. There was cervical adenopathy; the thyroid was moderately enlarged and quite firm. Tonsillectomy was advised and refused, but her condition improved with the subsidence of the tonsillitis, although her pulse remained at 136.

On January 23, 1924, her basal metabolic rate was +32.

The thyroid was still prominent; she had palpitation and dyspnea. She was very nervous and pulse ranged between 126 and 136; weight, 108 pounds. Four years ago her weight was 140 pounds.

Another attack of tonsillitis occurred on February 28, when all her symptoms of hyperthyroidism became exaggerated. Tonsillectomy was again advised but refused. The continuation of her symptoms during the next three weeks finally forced her to accept tonsillectomy. The tonsils, on removal, by culture showed Staphylococcus aureus. A bacterin was prepared and administered. During the following month there was a complete change in the clinical picture. The pulse promptly dropped to 80 and the weight gradually increased so that within seven weeks she weighed 126 pounds. Her pulse was 72; blood pressure, 110/75, with a basal metabolic rate of +8. There was very slight thyroid enlargement.

The patient has continued under observation and was last seen on February 8, 1926, when she weighed 124 pounds; she had taught in school since September, 1925, with no return of her former symptoms.

Summary. The necessity of a thorough search for foci of infection as a prerequisite to the successful treatment of many cases is emphasized.

The discovery of the relation of focal infection to many previously so-called constitutional diseases and degenerative processes is one of the great recent advances in medicine.

The opinion is expressed that the value of the removal of focal infection in the treatment of disease rather than being overdone is only just beginning to be appreciated.

Attention is called to the failure of some specialists, particularly dentists and rhinolaryngologists, to appreciate that a devastating focal infection may be present in the absence of demonstrable pus.

Periodic health examination is valuable as a means of discovering unsuspected foci of infection.

Overconfidence as to the end results of the removal of foci infection in the constitutionally defective individual must be guarded against.

The value of preparation and use of autogenous bacterins is discussed. A method of preparing them and their administration is indicated and an explanation of their action in focal infection is suggested.

Cases are cited to demonstrate:

1. The importance of the complete removal of all foci of infection.
2. The danger of multiple extraction of teeth.
3. The close relation of focal infection to gastro-intestinal diseases.
4. The influence of focal infection upon the thyroid gland and two cases reported which demonstrate that focal infection may influence the normal activity of the thyroid gland in either direction.

A CASE OF SPOROTRICHOSIS MENINGITIS.

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Introduction. We wish to report this case of chronic meningitis because the spores constantly found in the spinal fluid of the patient were morphologically similar to the sporotrichia of Schenck and de Beurmann. We feel satisfied that these organisms were the specific cause of the infection, and that our diagnosis was warranted, although we failed to obtain positive cultures and our animal inoculation experiments were inconclusive.

Sporotrichosis in man was first described by Schenck in 1898. Following him, de Beurmann and Gougerot reported several cases in 1900. Since then various reports have appeared, so that the disease has become well established and easily recognized clinically.

The infection is due to the sporotrichia, an organism allied to the hyphomyces. It is pathogenic for horses, dogs, rats, rabbits and guinea pigs. In man, it commonly produces skin lesions which are gummatous in character and may be mistaken for syphilitic or tuberculous lesions. The swellings are usually painless, slow in growth, chronic in nature, and they may either show a central necrosis, eventually breaking down with sloughing of the overlying skin, or they may resemble indolent ulcers.

The infection may become systemic, and it has been reported to have involved the lungs, bones, periarticular tissues, kidneys, and the eyes, causing miliary conjunctivitis and occasionally a panophthalmitis.

Involvement of the central nervous system in man has never been reported. Dominguez,[1] however, cites a case of an extradural abscess, complicating a sporotrichosis infection of the middle ear.

The organism is difficult to find in the tissues, but when present is pleomorphic. In smears from the tissues, the sporotrichia may be seen as round or oval bodies with dimensions from 1 to 2 micra by 3 to 5 micra, and appear occasionally in bacillus-like forms.

It grows at room or incubator temperature, and best in sugar media (dextrose, levulose and maltose). Sabouraud's medium is commonly used. It is also reported to grow in 1 per cent acid broth. First cultures may be slow in appearance and may not be visible for as long as two weeks. They are white or dirty gray on solid media, but if blood media are used, the cultures may be brown or black pigmented. Microscopically, the growth usually shows branching filaments, with spores in the filaments or in the

interspaces. Occasionally the filaments radiate as they do with actinomyces. Subcultures grow more luxuriantly.[2,3]

A definite diagnosis is made by positive cultures. Complement fixation, agglutination, and skin reaction tests have diagnostic value.

Iodides are specific for the disease.

Case Report. *Past History.* The patient was a girl, aged fifteen years, of American stock and a resident of Bayonne, New Jersey. She had had mumps, measles and scarlet fever, and in 1923 she suffered from what was called a mild attack of malaria. Menstruation began at the age of thirteen years, and was normal in character.

During the fall of 1924, she was in school and in perfect health. Just before Christmas she fell down a flight of stairs without injury other than bumping the back of her head; she was not even stunned.

Present Illness. On December 30, 1924, she became ill with nausea, vomiting, headache, generalized abodminal pain, and a fever which was not higher than 103°. In a few days, photophobia, weakness of the right side of the face and intense drowsiness developed. The fever disappeared after three or four days, but the nausea and vomiting continued, and her headaches were quite severe.

About January 15, 1925, diplopia, strabismus, and lancinating pains in the shoulders appeared. During the next month, symptoms fluctuated from day to day, with a trend toward improvement. The girl could not walk well, because of a tendency to stagger to the left, and any sudden change of position was apt to cause projectile vomiting. She was emotionally unstable, and had frequent nightmares.

She was examined in consultation on February 19. She seemed perfectly normal mentally, and coöperated well. The pulse was 100, there was no fever, and body nutrition was unimpaired. There were no signs of visceral disease.

She preferred to lie in bed, but could sit up comfortably if she moved carefully. With one eye covered she could walk perfectly well.

Cranial Nerves. There was obliteration of both optic disks and moderate engorgement of the retinal vessels; both pupils were large and irregular, but reacted to light and accommodation normally. The left external rectus muscle was completely, and the right was partially, paralyzed. There was a mild lower neurone type weakness of the right facial muscles. Otherwise the cranial nerves were normal.

Motor System.—All tests were performed well, except for a cerebellar incoördination in the left arm and leg.

Sensory System. No abnormalities were found.

Reflexes. Brudzinski and Kernig signs were positive. The arm and abdominal reflexes were normal. The knee and ankle jerks were abolished, and the plantar responses were sluggish and equivocal in type.

From February 19 to March 5 there was a steady improvement. There was almost no headache, no drowsiness, a decrease in vomiting, and she was able to get about the house. On March 5, a day or two after some difficulty in naming persons and objects had been observed, she vomited several times. While talking in the afternoon with some friends, she suddenly cried out, saying "I can't, I can't," and in a moment became flushed, clenched her arms and was unable to speak. In a few minutes she recovered sufficiently to get to her room. There was considerable vomiting for several hours, and it was 10.30 P.M. before she could express herself in speech. She seemed frightened, misnamed her mother, and talked incoherently of being cut and hurt. By the next morning, she was normal mentally and showed no aphasia, but there was considerable headache, and projectile vomiting occurred if she moved about in bed.

Examination on March 6 showed that there had been an improvement in the external rectus palsies with no change in the other abnormalities found at the time of the first examination. However, there were three new signs—a left partial ptosis, tinnitus in the left ear, and exudate in the left retina. The retinal vessels were moderately dilated, the disk was not visible, and radiating from the edges of the disk were large splashes of pure white exudate, extending outward into the retina a distance of perhaps two disk diameters. There was enlargement of the blind spot in the left eye, but no impairment of the visual fields. The right fundus was normal. There were no evidences of an aphasia or other residuals of the attack.

On March 10, another attack with confusion and a loss of speech occurred. The patient had been drowsy the day or two preceding. She was then admitted to the Neurological Institute.

Lumbar puncture was done, and about 40 cc. of fluid was drawn. It was clear and under intense pressure. Physical examination revealed increase in the right facial weakness, and much impairment of vision in the left eye, so that fingers could be counted only when held at a 6-inch distance. The neck was quite stiff. Otherwise there were no changes since the examination of March 6.

Blood count showed 21,000 white cells, of which 82 per cent were polymorphonuclear leukocytes. The urine was normal.

The spinal fluid contained two cells and 160 spores per cubic millimeter. Globulin and albumin were 2 +; and sugar, 68 mg. per 100 cc. Serological tests were negative. A smear of the centrifuged fluid, stained with methylene blue, showed abundant round and oval bodies which took the stain well and in many instances contained what seemed to be polar bodies. There were a few

phagocytes containing small inclusions, and an occasional lymphocyte (see Figs. 1 and 2). Cultures of this specimen of fluid were negative.

The bodies seen in the smear were identified by Dr. Anna Williams, of the Department of Health, as sporotrichia spores.

Within a few days, the left eye became blind. The patient had severe headache much of the time, and cerebral vomiting was frequent. Lumbar punctures were done at least once a day to relieve the meningeal irritation symptoms, and from 40 to 60 cc. of fluid was drawn each time with as a rule immediate improvement, lessening of the headache, decrease of the drowsiness, and cessation of vomiting. There was a slight fever, the rectal temperature varying between 99° and 101°.

During the next three weeks, no new clinical phenomena appeared, but there seemed to be periods of subsidence of all symptoms, alternating with periods of exacerbation lasting two or three days. With the increase of meningitic signs, the spinal-fluid pressure would be greater, there might be a slight fever, and the blood count would show a leukocytosis of from 14,000 to 20,000 cells, the polymorphonuclears ranging from 82 to 90 per cent.

On April 10, routine examination of the fundi showed an unusual picture in the left retina. Previously, the right retina exhibited a mild papilledema and slightly congested vessels, and in the left retina were the same splashes of peripapillary exudate that were first observed on March 6, dilated veins with occasional hemorrhages near the disk, and a nerve-head elevated about 4 diopters. Now to the temporal side of the left optic disk appeared a glistening pearly-white elevation, with borders serrated as are the edges of a cumulus cloud. This mass was 6 diopters in elevation, and across its surface ran small veins and arteries which dipped down at the edges and passed along with the retinal vessels. The retinal vessels were very tortuous, and there were large numbers of small hemorrhages scattered over the entire retina. This pearly-white mass seemed to be utterly unlike what one observes in a detached retina, and was regarded as of inflammatory origin.

With the exception of a period of two and a half weeks in April, the course of the disease seemed to be uninfluenced by any treatment. It was characterized by periods of relapse every seven to ten days, and in the last month by a gradual but steady increase in the signs of a posterior fossa meningitis. As a rule there was no fever, but during the relapses the temperature at times reached 101°. Death came on June 19, five months and three weeks after the onset of the illness.

From the clinical standpoint, there were several important features which must be considered.

From March 5 until the termination of the illness on June 19, a period of three and a half months, there were few new signs indicating extension of the disease process.

Roentgen ray of all the bones of the body showed no evidence of any infection with the sporotrichia. Roentgen ray of the gastro-intestinal tract was negative. The lungs showed a moderate degree of bronchial fibrosis. Cultures of saliva, sputum, naso-pharynx and tonsil smears, urine, blood and feces were negative for sporotrichia.

Roentgen ray of the skull revealed a thinning of the vault associated with a long-continued increase of intracranial pressure.

I. **Spinal Fluid.** The pressure of the spinal fluid was constantly and markedly increased. On one occasion manometric reading showed a pressure of over 600 mm. water. Lumbar punctures were done daily for therapeutic purposes.

Table indicates the variations in the fluid found on routine examination. As a rule from 40 to 60 cc. were drawn at each tap. There were only from 20 to 30 lymphocytes to the cubic millimeter, although the fluid was usually blood tinged and contained red cells in amounts from a few hundred to 2000 or 3000 per c.mm. The spinal fluid was as a rule more bloody during the relapses, which would last two or three days.

Following two intraspinal injections of sodium iodid, there was an exacerbation of meningitic signs and for a few days the spinal fluid contained about 5000 white cells per cubic millimeter of which nearly 100 per cent were polymorphonuclear cells.

Wasserman and colloidal-gold tests were negative. No tubercle bacilli were found at any time, and guinea pigs inoculated, showed no evidence of tuberculosis.

On standing at room temperature or in the incubator, the fluid would at times become opalescent. This phenomenon was unfamiliar to us and we were unable to determine its cause or chemical nature.

Hanging drop specimens from a large number of samples of spinal fluid were examined. In every specimen were visible small oval bodies which were approximately 2 or 3 micra wide and 3 to 5 micra long. These were refractile, and many of them seemed to contain at the smaller end what might be taken for a polar body. They exhibited a peculiar sort of motion. It was a combination of Brownian movement, with a revolving about the long axis of the body. This motility would decrease during examination and was not found when the spinal fluid had been standing for some time. The motility of these bodies was not due to convection currents, because the bodies would move about the field, whereas red or white cells would remain stationary. Occasionally one could see a macrophage, with an ameboid movement, and containing several dark round inclusions. The motile bodies were in a few instances paired end-to-end and once a chain of three was found. Perhaps half a dozen times rod-like forms with Brownian movement were seen.

TABLE—SPINAL FLUID ANALYSIS.

Color and date of appearance.	Lymphocytes per cubic millimeter.	Erythrocytes.	Globulin.	Sugar (per cent).	Hanging drop.	Stained smears.	Cultures.
March 10. Clear, colorless . . .	2	0	2+	0.068	160 spores	Spores, no other organisms	Negative to 21 days
March 13. Clear, few flocculi . . .	3	0	2+		40 spores	Negative	Negative to 21 days
March 14. Clear, colorless . . .	20	0	2+	0.068	20 spores	Spores	Negative to 21 days
March 15. Hazy, yellowish . . .	8	Many	2+		72 spores	Spores	Negative to 21 days
March 18. Hazy, yellowish . . .	9	A few	2+	0.051	Few spores	Spores	Negative to 21 days
March 19. Clear, colorless . . .	2	0	3+	0.088	Few spores	Spores	Negative to 21 days
March 21. Cloudy, fibrinous sediment	4600*	A few	4+	0.048	Few rods	Spores	Negative to 21 days
March 23. Yellowish, bloody . . .	Many	Many	4+		Spores and filaments	Spores and filaments	Mold contamination
March 26. Cloudy, blood tinged . .	25	Many	2+	0.040	Spores and rods	Spores and filaments	Negative to 21 days
March 30. Slightly hazy	....	....	....	....	Spores and rods	Large Gram-plus rods and spores	Negative to 21 days
April 1. Clear, colorless	0	Occasional	1+		Spores	Spores	Negative to 21 days
April 9. Clear, yellowish	20	Few	3+		Spores	Spores	Mold and Staphylococcus contamination
April 14. Hazy, yellowish	30	Many	2+	0.042	Spores	Spores	Negative to 21 days

* Seventy-seven per cent polymorphonuclears, 15 per cent lymphocytes, 8 per cent arachnoid mononuclears.

NOTE.—The spores were found easily in the hanging drop specimens, but with difficulty in smears of sediment or of supernatant portion of centrifuged spinal fluid. We cannot account for this. We neglected to vary the specific gravity of specimens of spinal fluid before centrifuging them.

Stained smears of the centrifuged sediment of spinal fluid were made. About twenty slides from as many different specimens of spinal fluid were examined (see Figs. 1 and 2). Careful search

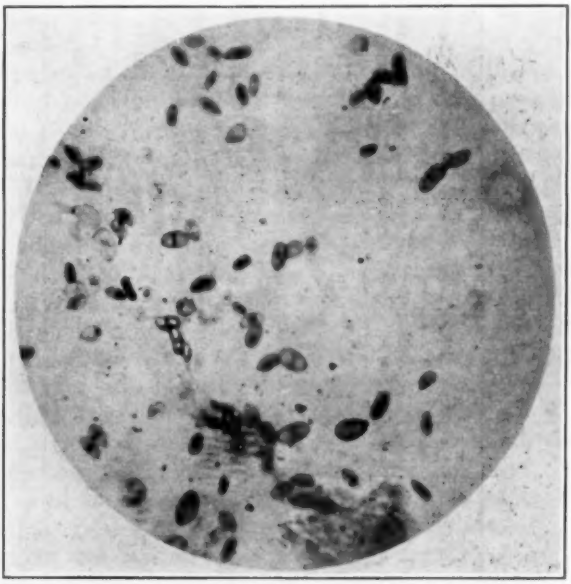

FIG. 1.—Spore forms in spinal fluid smear. (Methylene blue stain.)

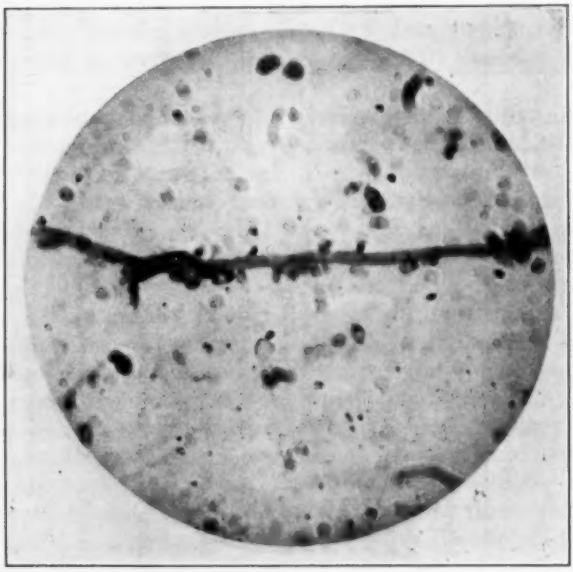

FIG. 2.—Spinal-fluid smear (oil immersion) showing mycelial filament and spores.

of each smear revealed in every instance the presence of spore-like bodies. Mycelial forms occurred in two or three of the smears. These bodies stained readily and were Gram amphophilic. Dr. Anna

FIG. 2a.—Spinal-fluid smear. Oil immersion × 10. Shows dividing form.

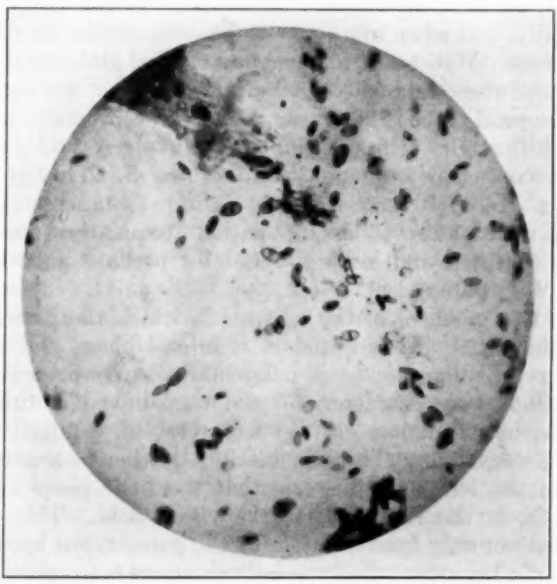

FIG. 2b.—Spinal-fluid smear. Shows spores, varying sizes and dividing forms.

Williams of the Department of Health regarded these bodies as belonging to the pathogenic molds, and stated that they were probably spores of the sporotrichia.

It was observed that these bodies were less numerous in the centrifuged sediment than they were in the hanging drop specimens made from fresh spinal fluid.

Cultures were made from many samples of the spinal fluid, in the laboratory of the Neurological Institute and also in the laboratory of Dr. Neal. Aërobic and anaërobic cultures were made and a large variety of sugar, blood and broth media were used in attempts to grow cultures at both incubator and room temperatures. We failed to secure any positive cultures. Both mold and bacteria-contaminating organisms were occasionally found. It is impossible to explain why these numerous attempts at cultures failed, especially when the sporelike bodies were constantly found in smears made of the centrifuged sediment of spinal fluid.

Dr. Elser (personal communication to G.H.H.), has observed one case of skin sporotrichosis in which positive cultures could not be obtained, and he considered it possible that iodid medication might have affected the organism so that it would not grow in culture.

II. **Tetanoid Attacks.** From March 16 to May 25, there occurred occasional mild attacks of tingling in the extremities, associated with spasm of the muscles of the hands, which assumed the accoucheur position. From May 25 until death, such attacks occurred almost daily, and when more severe there was extension of the legs and trismus. Myoclonic movements of the abdominal muscles accompanied these tetanoid attacks during the last few days of life.

III. **Temporal Lobe Phenomena.** The first occasion on which it seemed that the temporal lobe was involved was during the attack of confusion and aphasia on March 5. This attack and the one on March 10 were the most definite instances. However, in the last month of her illness, the patient frequently would become suddenly confused and lethargic, and for perhaps an hour would exhibit a mild paraphasia.

During two or three of the relapses in which the patient would become somewhat disorientated in time and place, and would be quite forgetful, microptic visual hallucinations were present. These hallucinations were characteristic and were linked in this patient with disturbed function on the left cerebral hemisphere. The reason for considering the hallucinations as due to a pathological process in the left hemisphere is that the little people appeared consistently in the right half of the visual field. This could be determined not only from questioning the patient, but by observing the patient's behavior when the hallucinations were present.

IV. **Treatment.** When it seemed that we were dealing with a sporotrichosis infection we began intensive iodid therapy. From about March 15 until May 20, the patient received from 60 to 150 gr. of sodium iodid a day. During March it was given intravenously as well as by mouth, twice it was administered intraspinally. The intraspinal injections caused a good deal of pain, and also produced a rather severe aseptic meningitis. A few injections of salvarsan were given over a period of three weeks in May

and early June. Quinin was given in March and discontinued after two or three days because the patient did not tolerate it. It was tried again after the iodids were discontinued and had to be given up for the same reason.

In addition to the above drugs, symptomatic remedies were used. Of these, retention enemas of 25 per cent salt solution seemed definitely helpful in relieving the vomiting which was much more frequent during the relapses, and at the times when the spinal-fluid pressure was greatest.

Since the sporotrichosis infection produces granulomatous lesions, since we were dealing with a very serious situation, and since it has been observed that intravenous administration of a solution of active deposit of radium emanation has at times had therapeutic effect in Hodgkin's Disease, we felt justified in trying an experiment.

On April 2, the patient was given intravenously 70 millicuries of active deposit solution of radium emanation. At the time this was given the patient had been moderately deaf for about two weeks, so that whispers could not be heard and the patient was unable to hear the children singing in a nearby school, or detect the sounds of people passing through the corridor by her room. She had a bilateral facial weakness, there was right internal strabismus, and the signs of meningeal irritation had been troublesome for several days.

The injection was given at 1.30 P.M. At 3 P.M. the patient vomited twice. At 4 P.M. tenderness and swelling of both parotid glands appeared. By 6 P.M. the swelling had extended to the submaxillary glands and also involved the lateral and posterior cervical lymph nodes. The patient was also quite drowsy and complained bitterly of a stiff neck. During the night she observed to the nurse that she was again able to hear sounds which she had been unable to hear for a week. The next morning, the meningeal signs were markedly reduced and less than they had been for some days. During the next few days the salivary glands and lymph node swelling disappeared, the eye movements were better, the facial weakness improved, and the spinal fluid gradually became free of red blood cells and the sporelike bodies became scanty in numbers. From about April 10 to 30, the patient's general condition steadily improved and the cranial nerve signs also lessened. The patient became able to walk about the room, stay up most of the day, and even took a few rides about the town in an automobile.

During May when the patient had become worse, another dose of active deposit was given. The same swelling of the salivary glands ensued, and there was also a mild systemic reaction with a temporary exacerbation of the meningeal signs. However, this injection was not followed by the clinical improvement which occurred after the first injection.

It is interesting to speculate upon the phenomena following the

first injection. In particular, the swelling of the salivary glands was noteworthy. This complication has not been observed in a series of several hundred intravenous injections of radium deposit at the Memorial Hospital in New York. It is conceivable that the glands became swollen because they were the avenue of entrance of the sporotrichia infection, and, therefore, were already predisposed to the reaction which would be a consequence of the radium attacking infected tissues.

It is also conceivable that the radium in producing a systemic reaction upset the vegetative function, and caused a temporary disturbance in the gonads. The injured gonads may have then caused a selective sympathetic involvement of the salivary glands, exhibiting in the reverse fashion the relationship between the salivary glands and the gonads, well known in mumps.

Necropsy. A complete necropsy was done six hours after death.

Examination of the viscera showed no abnormality other than might be found due to agonal causes, and nothing which would throw light on the lesions in the central nervous system. The skin showed no lesions of any description, and the mucus membranes were normal with the exception of a mucopurulent conjunctivitis in both eyes. This appeared a few days before death.

The gross pathology was limited to the intracranial cavity. Protocol of the examination of the head and intracranial cavity follows:

Head. Symmetrical and not enlarged. Scalp and pericranium negative. Dura slightly adherent to calvarium; latter thin over vertex. Sutures quite visible. Superior longitudinal sinus empty. Dura everywhere appears normal.

Brain. No bulging. Cerebral hemispheres apparently symmetrical. Veins moderately prominent, but there is no marked convolutional capillary congestion. Convolutions over vertex somewhat flattened and sulci compressed. Pacchionian bodies small. Piaärachnoid over parieto-temporal regions semiopaque and slightly thickened. Cerebellar convolutions fairly well obliterated, particularly on the left side. There is considerable cloudy, bloody fluid in the subtentorial space. Base of brain shows widespread subarachnoid accumulation of cloudy fluid—well marked between the cerebellar hemispheres, where a gelatinous mass 5 by 1½ by 1 cm., is seen. The piaärachnoid appears thickened over the inferior surface of the cerebellum and in the interpeduncular space. An occasional small area of hemorrhage is seen in the leptomeninges over the base. No granulomatous tissue, abscess formation, or softening of the cortex observed. There is a gelatinous exudate about the left optic nerve, and in the left orbit, where there is also considerable edema of the orbital fat. Retinæ were not removed.

There is slight internal hydrocephalus as determined by puncture

of the ventricles, 10 cc. being withdrawn from the left and 5 cc. from the right. Fluid slightly hazy.

The ethmoid, sphenoid, frontal and mastoid sinuses and the middle ears were opened and were all found to be perfectly normal and free of any fluid, mucus, or inflammatory thickening of the membranes.

On section, after hardening in 10 per cent formalin, the brain showed softening of both basal ganglia, probably postmortem. There was a very marked thickening of the piaärachnoid and of the ependymal lining of the ventricles. The spinal cord was not removed.

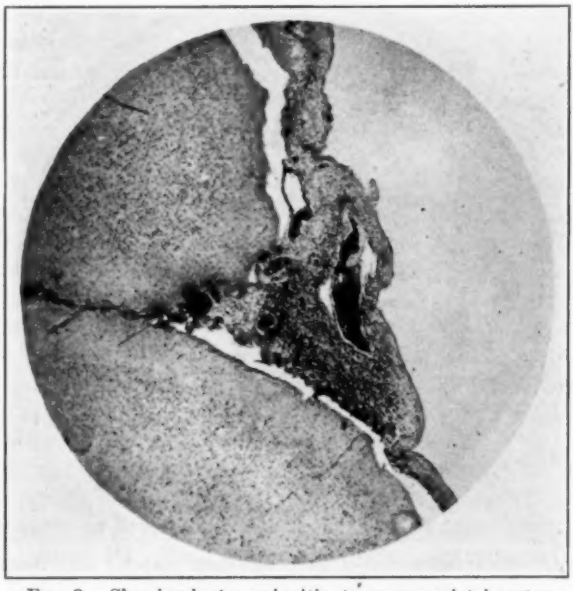

FIG. 3.—Showing leptomeningitis, temporo-parietal cortex. (Hematoxylin-eosin stain).

Anatomic Diagnosis. Chronic diffuse leptomeningitis, with gelatinous exudate beneath piaärachnoid. Exudative periophthalmitis and perineuritis (left).

Histologic Examination. [Stains: Hematoxylin and eosin, Mallory, Nissl, van Gieson and Loyez (myelin)].

Temporo-parietal Area. There is a marked thickening of the piaarachnoid with increase of connective tissue and great infiltration of the pia with numerous lymphocytic and plasma cells (Fig. 3). In the cortex there is well-marked perivascular edema with occasional scattered round cells in the Virchow-Robin spaces (Fig. 4). There is edema of moderate degree in the outer layers of the cortex,

but no hemorrhages. No degenerative changes of ganglion cells beyond scattered very slight swelling of isolated cells in the outer layers of the cortex. No glia proliferation. In the subcortical region there are numerous intraglial foci filled with metachromatic lipoids, but there is no degeneration of the myelin sheaths.

Cerebellum. The picture of the meninges covering the cerebellum is similar to that described (cerebral). The perivascular edema within the cerebellum is of minor degree with absence of cellular infiltration. Foci of the mycelium forms with spore inclusions were found in the meninges covering the cerebellum.

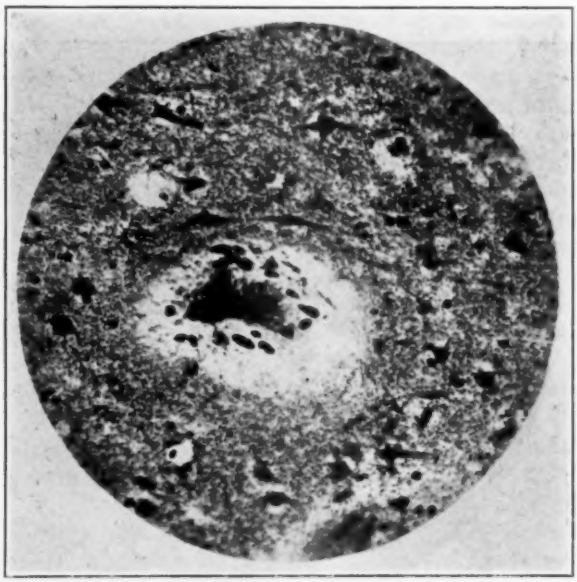

FIG. 4.—Perivascular infiltration of temporoparietal cortex. (Rio Hortega stain.)

Medulla. The leptomeningitis is also found surrounding the medulla oblongata. The Loyez (myelin) stain shows swelling of the myelin sheaths throughout the whole section, most pronounced at the periphery where transitions to partial myelin sheath degeneration and complete loss of myelin sheaths are noticed.

Histologic Diagnosis. Severe chronic leptomeningitis and low-grade cerebral edema.

Animal Inoculations. The animal inoculations were carried out in the laboratory of Dr. Josephine B. Neal. The results follow:

A. **From Spinal Fluid of Patient.** *Mice.* March 19. Two mice injected intraperitoneally; mice living three months later.

March 29. Three mice injected intraperitoneally. One mouse living, two mice on necropsy two weeks later had tapeworm and also showed enlarged and reddish lymph nodes, adherent viscera

and deposits of gelatinous substance in the peritoneum. Cultures negative.

March 22. Three mice injected intraperitoneally. One died of pneumonia, one died of brain hemorrhage and one died of causes unknown.

April 14. Nine mice injected intraperitoneally; living four months later.

Guinea Pigs. March 19. Two guinea pigs injected intraperitoneally. Both died of pneumonia and cultures showed pneumococci.

March 20. Two guinea pigs injected intraperitoneally. One of the guinea pigs died of tuberculosis.

March 22. Two guinea pigs injected intraperitoneally. One guinea pig showed on necropsy enlarged inguinal and axillary lymph nodes and peritoneal and pleural fluid; cultures were negative. The second guinea pig on necrospy showed mottled lungs, normal kidneys and liver, and gelatinous masses in the peritoneal cavity. Cultures were negative.

June 9. Two guinea pigs injected intracranially. One died in twenty-four hours presumably of shock; the other guinea pig is alive.

Rabbits. June 9. Two rabbits injected intracranially. Both rabbits died of septicemia which was passed to subculture guinea pigs. The cultures showed cocci and bacilli.

B. **Ventricular Fluid (Postmortem on Patient).** June 19. Three guinea pigs injected intraperitoneally. One guinea pig is alive. Another guinea pig died July 11; the brain was found to be congested. Cultures negative. The third guinea pig died July 8 and showed congested brain and lungs; cultures were negative.

Subcultures on two guinea pigs from this third animal gave negative results.

C. **Emulsion of Brain Swabs of Gelatinous Exudate (From Brain of Patient).** June 19. Four rabbits injected intracranially. Two died of injection shock; one died of septicemia which was passed to guinea pigs; one at death showed hemorrhage of the brain, cultures of which were negative.

June 19. Three guinea pigs injected intraperitoneally. One is alive, another guinea pig died in September of pneumonia, and a third died three days after inoculation. Necropsy was not done.

D. **Résumé of Experimental Work.** Six rabbits, 14 guinea pigs and 17 mice were inoculated. Of these, 2 mice, and 1 guinea pig, which were inoculated intraperitoneally with spinal fluid from the patient, showed a gelatinous exudate in the peritoneal cavity. This exudate was in appearance similar to that found under the meninges of the patient.

Inoculations of postmortem material from the patient gave results which were not helpful.

Examination of the gelatinous exudate found in the mice and guinea pigs revealed no organism.

Histologic study of postmortem material of inoculated animals was not helpful and corroborated the clinical diagnosis as to cause of death only.

Summary. Sporotrichosis infection of the nervous system has not been observed previously.

Our patient was a girl, aged fifteen years, who became ill December 30, 1924, and died June 19, 1925. The infection involved the posterior fossa largely, had a febrile onset, and ran a chronic remitting course. There were slight exacerbations about every ten days, accompanied by a slight fever.

Interesting clinical occurrences were tetanoid attacks, microptic hallucinations, and several temporosphenoidal seizures.

The diagnosis was made by the presence of sporotrichia spores and mycelial forms in the spinal fluid.

Iodid therapy was of no avail. Experiments with radium intravenously gave interesting results.

Culture and animal inoculation results were negative.

Microphotographs of the spores seen in the spinal fluid and of the tissue from the patient's brain are exhibited.

Autopsy of the patient showed a chronic diffuse leptomeningitis most marked in the posterior fossa, a moderate edema of the brain and the presence of a peculiar gelatinous exudate here and there beneath the pia. Microscopically, there was shown a chronic productive leptomeningitis but no inflammatory involvement of the brain substance.

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MENINGITIS CAUSED BY BACILLI OF THE COLON GROUP.

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Meningitis caused by organisms of the colon group is comparatively rare. In analyzing more than 1500 cases of meningitis seen by the Meningitis Division of the Research Laboratory up to 1924, only 5 cases were found due to the Bacillus coli in pure culture. A sixth case was due to a mixed infection, one of which was a member of the colon group. There were 2 cases caused by Friedländer's bacillus.[1]

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The following table shows the cases collected from the literature and also our own cases:

TABLE I.—CASES OF MENINGITIS CAUSED BY BACILLI OF COLON GROUP.

Source.	Year.	Organisms.	Number cases.	Remarks.
Lloyd[2]	1898	Bacillus coli	1	
Concetti[3]	1900	Bacillus coli	4	
Nobecourt and Du Pasquer[4]	1902	Bacillus coli	1	
Kolle and Wassermann[5]	1903	Bacillus coli	13	
Braillon and Merle[6]	1914	Bacillus coli	1	
Milner[7]	1915	Bacillus coli	1	
Michael[8]	1916	Bacillus coli	1	
Frank[9]	1916	Bacillus coli	1	
Barron[10]	1918	Bacillus coli	11	3 additional cases in Kolle and Wassermann.
Sickenga and Munk[11]	1924	Bacillus coli	1	
Meningitis Division[1]	1925	Bacillus coli	6	1 mixed infection.
Total Bacillus coli			42	
Guinon and Simons[12]	1910	Friedländer's bacillus	1	
Bonhoff and Esch[13]	1912	Friedländer's bacillus	1	
Kolle and Wassermann[14]	1913	Friedländer's bacillus	10	
Haig[15]	1919	Friedländer's bacillus	2	
Elias[16]	1924	Friedländer's bacillus	2	
Menetrier and Bertrand-Fontaine[17]	1924	Friedländer's bacillus	1	
Lion and Minvielli[18]	1924	Friedländer's bacillus	1	
Meningitis division[1]	1925	Friedländer's	2	
Total Friedländer's bacillus			20	
Beitzke[19]	1904	Bacillus lactici aërogenes	1	
Kolle and Wassermann[14]	1913	Bacillus lactici aërogenes	2	
Total B. lactici aërogenes			3	
Greenthal[20]	1921	Bacillus acidi lactici	1	
Sherman[21]	1922	Bacillus acidi lactici	1	
Ray[22]	1923	Bacillus acidi lactici	1	
Total B. acidi lactici			3	
Total colon group			68	

Barron,[10] in a careful study "Meningitis in the Newborn and in Infancy," found that in 42 cases, 39 of which were under three months of age, there were the following classified according to etiology:

TABLE II.

Bacillus coli	14
Streptococcus and staphylococcus	10
Meningococcus	5
Pneumococcus	4
Tubercle bacillus	3
Bacillus mucosus capsulatus	1
Bacillus influenzæ	1
Bacillus typhosus	1
Bacillus lactis aërogenes	1
Bacillus pyocyaneus	1
Bacillus catarrhalis (?)	1
	42

All except 1 of these cases were collected from the literature. In the earlier cases the diagnosis was often made at necropsy and it seems probable that in many instances the Bacillus coli may have been an invader just before or just after death and not the specific cause of the meningitis. Certainly this distribution by etiology is in marked contrast to that in 50 cases of our own in infants during the first three months of life, which is as follows. In this list the diagnosis was made by the examination of the spinal fluid, and the meningococcus was by far the most frequent cause.

TABLE III.

Meningococcus	24
Streptococcus	11
Tubercle bacillus	5
Pneumococcus	3
Bacillus coli	3
Bacillus influenzæ	2
Micrococcus catarrhalis	1
Streptococcus hemolyticus and Staphylococcus albus	1
	50

As the typhoid group is so closely allied to the colon group it may be mentioned that we have had only one case in which any member of the typhoid group was involved. This was originally a case of Meningococcus meningitis but the paratyphoid Bacillus appeared in the fluid during the course of the illness. The case was reported by Appelbaum.[23] A very complete study of typhoid meningitis was made by Bayne-Jones[24] in 1917.

The following table gives certain data in regard to our cases:

TABLE IV.

Year.	Case No.	Age.	Sex.	Primary focus.	Approximate duration.	Outcome.
				FRIEDLANDER'S BACILLUS.		
1915	38	2½ yrs.	M.	Pneumonia and otitis media	About two weeks with meningitis	Recovery.
1920	221	59 yrs.	M.	Otitis media	Six days	Died.
				BACILLUS COLI.		
1923	29	2 wks.	M.	Not determined	Twelve days	Died.
1920	360	5 wks.	M.	Not determined	About 8 weeks	Recoved from meningitis developed hydrocephalus died almost a year later.
1923	151	8 mos.	F.	Pyelitis	About 3 weeks	Died.
1916	665	1½ yrs.	M.	Not determined	About 4 weeks	Died.
1919	316	6 yrs.	F.	Infection of orbit	Eight days	Died.

As these cases are comparatively rare a brief description may be of interest.

Case Reports. CASE XXXVIII.—W. S., a boy, aged two years and seven months, was admitted to Willard Parker Hospital March 20, 1915. The onset of the illness on March 19 had been sudden, with a fever of 104° F. He had quickly become stuporous. When examined on March 20 the temperature was 104° F., pulse, 160; respiration, 40. There was a slight stiffness of the neck, a positive Macewen sign, and Kernig sign, no Brudzinski or contralateral reflex. The patellar reflexes were exaggerated, the eyes were normal; there was a discharge from both ears and tenderness around the right mastoid. He was somewhat stuporous. On lumbar puncture 50 cc. of turbid fluid were withdrawn and 25 cc. of antistreptococcus serum were injected, as the meningitis was apparently secondary to the ear involvement. The fluid showed a very great increase in cells, 95 per cent polymorphonuclears, a moderate increase in the albumin and globulin and a normal sugar content. No definite organisms were found in the smear and it was thought that the culture was contaminated. On March 21, 50 cc. of blood-stained fluid were withdrawn and 20 cc. antistreptococcus serum injected. This fluid showed much the same picture as the first, but a Gram-negative diplobacillus (Friedländer's) was cultured from the fluid, also a diphtheroid bacillus, thought to be a contamination. The patient's general condition was slightly better, but at this time ptosis of the left eyelid appeared, together with dilatation of the left pupil and paralysis of the third nerve on the left side. On March 22, 50 cc. of blood-tinged fluid was obtained. This fluid was sterile as were also the fluids withdrawn on March 22, 24, 25 and 27. These late fluids showed a progressive decrease in the number of cells and in the protein content. The patient's condition also improved. On March 24 an autogenous vaccine was given for the first time in a dose of 250 million. As the spinal fluid had already become sterile, the vaccine cannot be given the credit for the cure of the meningitis. During convalescence from the meningitis a pneumonia with a positive blood culture developed, and an operation on the mastoid was performed. The patient eventually made a complete recovery.

CASE CCXXI.—Father S., an Italian priest, aged fifty-four years, was seen on June 12, 1920. He had suffered from diabetes and nephritis for several years and from a slight right facial paralysis for some time. Three months before, an acute otitis media had developed. He had been taken

ill very suddenly on June 7, with vomiting and chilly sensations. He became unconscious within two hours. There had been no fever for the first two days of his illness. When examined on June 12 he had a temperature of 102° F., pulse, 78; respiration, 46. There was moderate stiffness of the neck and Kernig sign.

The pupils were equal and reacted to light. The patellar reflexes were absent. At times he was delirious and at times stuporous. On lumbar puncture 50 cc. of cloudy yellow fluid were obtained and 20 cc. of antimeningococcus serum injected. The fluid showed an enormous increase in cells, practically all polymorphonuclears, a great increase in the albumin and globulin, and no sugar. In the smear there were numerous short Gram-negative diplobacilli both intracellular and extracellular. A pure culture of Friedländer's bacillus was grown. The patient died on June 13.

Of the cases due to the colon bacillus the second was of unusual interest and will be described last in more detail. The others briefly were as follows:

Case XXIX.—Baby S., aged two weeks, was seen January 30, 1923. The baby had vomited at times since birth and there had been greenish stools. It was difficult to tell when the meningitis had first appeared as meningeal symptoms in infancy are so indefinite. The physician in charge of the case thought it had lasted for about a week. When examined on January 30, the temperature was 100° F., the pulse rapid but regular. The fontanel was bulging, the pupils were equal and reacted to light. The other reflexes were difficult to obtain. As in all infants in the earlier stages of meningitis the stiffness of the neck and Kernig sign were absent. On lumbar puncture 30 cc. of cloudy fluid were obtained and 15 cc. of antimeningococcus serum were injected. The fluid showed an increase in cells, practically all polymorphonuclears, a great increase in albumin and globulin, and an absence of sugar. In the smear there were many short Gram-negative bacilli. A pure culture of colon bacillus was grown. These findings were practically the same in the subsequent fluids. On January 31, 5 cc. of blood-tinged fluid were obtained by lumbar puncture and on February 2, 0.5 cc. of very purulent fluid. On February 3 and 4 ventricular punctures were done, yielding 45 cc. and 10 cc. respectively of purulent fluid. On February 15, the patient's condition was so serious that no puncture was done. Death occurred on the afternoon of February 15.

Case CLI.—B. T., female infant, aged eight months, was seen on April 23, 1923. The onset of the illness was five days before with fever of 104° F., vomiting, convulsions, cough and irritability. There was a serous discharge from the right ear. There was no stiffness of the neck. The Kernig and Brudzinski signs were negative. The fontanel was not bulging. The pupils were equal and reacted to light. The patellar reflexes were normal. There was marked congestion of the pharynx. The heart and lungs were normal. The spleen was slightly enlarged. The temperature was 101° F., pulse, 120; respiration, 34. As the meningeal symptoms were indefinite no puncture was done. On April 24, as the condition was not improving, a lumbar puncture was performed, 15 cc. of clear fluid being withdrawn. This fluid showed a moderate increase in cells, 90 per cent mononuclears. The protein and sugar were normal and there were no organisms by smear or culture. It was thought that the condition was one of meningism, probably secondary to the otitis media. The child's condition did not improve and a second puncture was done April 27, yielding 30 cc. of slightly blood-tinged fluid. This fluid was apparently normal except for the blood present. On May 5, a third puncture was done, 20 cc. of clear fluid being withdrawn. This

fluid was normal except for a very slight increase in mononuclears and in protein. A week later the child seemed worse and showed more evidence of meningeal involvement. On lumbar puncture May 12, 3 cc. of very purulent fluid were withdrawn. This fluid showed a very great increase in cells —polymorphonuclears—and in protein and no sugar. Numerous short Gram-negative bacilli were found in the smear and a pure culture was grown of motile, Gram-negative bacilli which fermented, with the formation of acid and gas, dextrose, mannite, maltose, lactose, dulcite and saccharose. This identified the organism as Bacillus coli communior. Later the patient was catheterized and a pure culture of the same organism was isolated from the urine. We, therefore, concluded that the meningitis was secondary to the pyelitis. Lumbar punctures were done daily until May 18 when it was necessary to do a ventricular puncture as but a few drops of fluid could be obtained from the spine. The ventricular fluid was sterile. On May 19, no fluid could be obtained from the spine but the general condition was somewhat better. On May 21 the child was somewhat more restless and the temperature was higher 103.5° F. A second ventricular puncture was done yielding 20 cc. of blood-tinged fluid which was sterile. On May 24 a little thick blood-tinged fluid was obtained from the spine. This was also sterile. A catheterized specimen of urine was much less cloudy. The temperature was normal and the general condition seemed much better. This improvement continued until the night of May 26 when convulsions began. A ventricular puncture on May 27 yielded 35 cc. of purulent fluid containing large numbers of organisms. The child died on May 28.

Case DCLXV.—E. D., a male infant, aged one and a half years, was first seen on October 22, 1916. There had been a sudden onset, with high fever on October 8. There had been no vomiting. On examination the child was stuporous; the neck was stiff and there was a positive Kernig sign. The Macewen sign was very marked. The patellar reflexes were normal. The temperature was 104° F. On lumbar puncture 40 cc. of turbid fluid were withdrawn and 20 cc. antimeningococcic serum given. This fluid showed a great increase in cells—polymorphonuclears—and in protein and a very low sugar content. In the smear a few Gram-negative "cocci" were seen but the culture was sterile. A second puncture was done on October 23, 20 cc. of fluid being withdrawn and 20 cc. of serum being given. The findings in the second fluid were identical with those in the first. The parents refused further treatment and the case was removed to a hospital where the serum treatment was continued. It was seen by us at the hospital on November 17, when 5 cc. of purulent fluid were obtained by lumbar puncture. This showed numerous short, thick, Gram-negative bacilli in the smear and a pure culture of the colon bacillus. The child died a few days later. It is impossible to say whether this was originally a meningococcus infection or whether the cocci seen in the first two smears were very short bacilli. Organisms in spinal fluid often show pleomorphic forms and we, therefore, feel that we can rely very little on morphology. Of course, the failure of the organism to grow would be more in favor of the meningococcus as the colon bacillus grows far more readily.

Case CCCXVI.—M. K., a girl, aged six years, was first seen December 10, 1919. She had had measles in May. Following this an abscess had developed behind the right eye necessitating the enucleation of the eyeball. She had complained of pains in the right ear for about a month and had seemed tired and irritable for several days. There had been vomiting for four days. She had been worse on the night of December 9, with fever. When examined she was somewhat irritable, there was moderate stiffness

of the neck and a marked Kernig and Macewen sign. The pupil was dilated but reacted to light. The patellar reflexes were absent. There was some tenderness over the right mastoid. The eye socket showed some inflammation. There was profuse sweating. The temperature was 102° F., pulse, 120; respiration, 34. On lumbar puncture 40 cc. of cloudy fluid were withdrawn and 20 cc. of antimeningococcic serum administered. This fluid showed a great increase in cells—polymorphonuclears— and in protein and no sugar. The smear was apparently negative but the culture showed a few colonies of Bacillus coli, which were considered a contamination. Lumbar punctures were done and serum was administered on December 11, 12 and 13. The child's condition improved. The spinal fluids were sterile, became clearer, showed a dimunition in the protein and an increase in the sugar. On December 14 and 15 the general condition was not so good and the temperature rose. On December 16 the temperature was 105° F. and the pulse, 160. A lumbar puncture yielded 50 cc. of very purulent fluid from which the colon bacillus was again isolated, this time in great numbers. It seemed probable that a nonspecific action of the serum had produced a temporary control of the infection and an amelioration of the condition. I have seen this same occurrence in other cases of purulent meningitis. The child died on December 17.

Case L. S.—By far the most interesting case in the series was that of L. S. He was born on October 6, 1920. The delivery was normal but he showed signs of collapse and difficulty in breathing for about ten hours. He had slight twitchings for the first few days but these ceased and he seemed normal except for signs of a patent foramen ovale, until the onset of his illness, November 2, 1920. His weight at that time was 10 pounds 7½ ounces. He had weighed 10 pounds 3 ounces at birth. The early symptoms were rather indefinite—sight twitchings, vomiting, a temperature ranging from subnormal to 101.5° F. Early on the morning of November 7, he had a severe convulsion and was seen in the evening of that day. At that time he was in a stuporous condition, the head was thrown back, the fontanel was bulging, the patellar reflexes were not elicited. He was taking nourishment badly and was vomiting profusely. The temperature was 101° F., pulse, 160 and poor in quality. A lumbar puncture had been done by another physician earlier in the day and 5 cc. of purulent bloody fluid had been obtained. He had reported that meningococci was present in the smear. A second lumbar puncture was done yielding 3 cc. of purulent, sanguinous fluid and as there were marked pressure symptoms a ventricular puncture was done, 45 cc. of very purulent sanguinous fluid were withdrawn and 20 cc. antimeningococcic serum injected by gravity. This fluid was uniformly sanguinous and was the most purulent that we have ever received at the laboratory where over 12,000 fluids have been examined. When a test tube full was allowed to stand only a thin layer of clear fluid appeared at the top; over nine-tenths was thick pus. The child's condition was so precarious that it seemed doubtful if it would live until morning. The examination of the fluid showed an enormous increase in polymorphonuclear cells and in protein and an absence of sugar. In the smear there were numerous short, thick, Gram-negative bacilli which grew in pure culture. These organisms fermented lactose and dextrose with production of gas and formed indol, thus proving that it was Bacillus coli communis. On November 8, the condition was slightly improved. The convulsions were less frequent and nourishment was being taken better and retained. On ventricular puncture about 40 cc. of fluid similar to the first were withdrawn and 20 cc. of antimeningococcic serum again given as the organism had not yet been determined. On November 9, the baby was having slight convulsive seizures and the pulse was of a poor quality. A ven-

tricular puncture was done, removing 40 cc. of similar fluid, and 20 cc. normal saline were injected into the ventricle as it seemed safer to do so since so much fluid had been withdrawn. Ventricular punctures were done daily, with one or two exceptions, until November 28, after which a puncture every other day seemed sufficient. Beginning November 18, several doses of autogenous vaccine were given in the ventricle with the saline, as the fluid showed no signs of clearing and vaccine treatment is often beneficial in Bacillus coli infections. The baby's general condition was gradually improving. On November 12, it cried for the first time. The vomiting was less frequent and the feedings were taken better. The pulse became better in quality and somewhat slower in rate. The temperature was usually between 99° and 100° F. The fluid, however, remained under greatly increased pressure and very purulent although it became less sanguinous. The amount withdrawn varied from 30 to 60 cc. The ventricles were usually injected with saline at each puncture. The findings in the fluid were the same as at the first puncture, except that the growth of the organism became less profuse. Finally the twenty-fifth fluid, withdrawn December 9, was sterile, as were all the fluids thereafter. On December 11, the fluid was conspicuously clearer and showed the presence of sugar for the first time. On December 15, a lumbar puncture was done and 8 cc. of clear fluid obtained. Another lumbar puncture was done on December 18. On December 20 as there were facial twitchings (these had been present earlier but had been absent for over a week) and vomiting, both ventricles were punctured to make sure that there was no intracranial pressure. From the right ventricle 4 cc. of clear fluid were removed and from the left 1 cc. Lumbar punctures were done also on December 23, 26, 29 and January 5.

The temperature was normal after November 27 and the pulse was usually about 120 and of good quality. The general condition improved very satisfactorily. On December 3 the baby's weight was 9 pounds. He gained steadily thereafter until it reached 12 pounds 6 ounces on February 6. The baby slept well, was playful and intelligent, and seemed entirely normal. The head was slightly enlarged, as was to be expected after the prolonged period of increased pressure. At times the fontanel seemed somewhat tense but this lasted only for a short time and did not occur frequently. Finally, however, about March 10 the head began to enlarge rapidly. On March 13, a lumbar puncture was unsuccessful and 60 cc. of clear fluid were withdrawn from the ventricle. This fluid was normal except for a slight increase in protein. The relief afforded by the puncture was only temporary. Another ventricular puncture was done March 19 and 60 cc. of clear fluid again removed. A suggestion that the baby be taken to a hospital to try operative measures was not acted upon. The hydrocephalus continued and the baby died about 9 months later.

Children under six months of age, suffering from meningitis are particularly prone to develop a subacute arachnoiditis. This is what probably happened in this case—the inflammation continuing and finally completely cutting off the foramen of Magendie. I have seen a similar occurrence in cases of epidemic meningitis when, after ventricular punctures and the intraventricular administration of serum have rendered the ventricular fluid sterile, one or two lumbar punctures have been successful. But in these cases the complete blocking has taken place in a few days, and the duration of the hydrocephalus has been short, death occurring in at most a few weeks.

Conclusions. 1. Meningitis due to members of the colon group is comparatively rare. In studying over 1500 cases of meningitis only 7 were found due to these organisms. In an eighth case there were several organisms present, one of which belonged to this group.

2. Meningitis in the first three months of life is most often caused by the meningococcus—24 out of 50 cases being due to this organism and only 3 to the Bacillus coli.

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REVIEWS.

PUBLIC HEALTH LAW: A MANUAL FOR SANITARIANS. By JAMES A. TOBEY, M.S., LL.B. Pp. 314. Baltimore: Williams & Wilkins Company, 1926. Price, $4.50.

THE legal side of public health, the law-making powers of our governmental units and the police power of health organizations are explained. The state and local health organizations and their powers are treated fully, especially as relating to school hygiene, vaccination, milk, foods and drugs and the control of communicable diseases. Nuisances are defined and their abatement and prevention discussed. Social hygiene, mental hygiene, health legislation and law enforcement are discussed in detail.

Throughout the work there are numerous references to the recent literature and to rulings of the courts on cases relating to the subject under discussion.

This is a valuable book for all public health officials.

D. B.

MUSCULAR ACTIVITY. By ARCHIBALD VIVIAN HILL, University College, London. Pp. 115; 12 illustrations. Baltimore: Williams & Wilkins Company, 1926. Price, $2.75.

THE Herter Lectures given by the author in 1924 are here printed, and they supply an excellent summary of the very important work that he and his coworkers have carried out. While new problems are raised as to the actual mechanism of muscular contraction, some of the phenomena accompanying it receive already a rational explanation. Throughout the muscle is assumed to be working at the expense of carbohydrate and the question of fat metabolism is dismissed in a few words, as a problem at present unsolved.

H. B.

RECENT ADVANCES IN PHYSIOLOGY. By C. LOVATT EVANS, M.D., University College, London. Pp. 364; 69 illustrations. Philadelphia, P. Blakiston's Son & Co., 1926.

THIS volume is small, but terse and compact, readable and not unduly mathematical. Although not meant to be a "medical"

physiology, it considers matters like the once-obsolete "buffy coat," whose physiologic importance has recently been emphasized. About half the book deals with the blood and the circulatory system, discussing gases, buffers, cardiac dynamics, capillary physiology and surgical shock, etc. The rest of the book treats of the mechanism of tissue oxidation, physical and chemical aspects of muscle contraction, internal secretions and reflex functions. Although a few of the points treated here are not strictly "recent," the book will be found a useful supplement to the regular textbooks.

L. T.

MEDICINE MONOGRAPHS. VOL. VII. LEAD POISONING. By JOSEPH C. AUB, LAWRENCE T. FAIRHALL, A. S. MINOT and PAUL REZNIKOFF. Pp. 265; 35 illustrations. Baltimore: Williams & Wilkins Company, 1926. Price, $4.00.

THIS latest *Medicine Monographs* includes a critical review of the chemical, physiologic, pathologic and clinical aspects of lead poisoning, but more important is the account of the series of well-planned experiments done at the Harvard Medical School. These have served to elucidate the many obscure problems of lead poisoning, but most significant is the rationalization of the treatment of lead poisoning which makes the work reported one of the distinctive research contributions of the past ten years.

Specifically the chapters on the chemistry and physiology of lead intoxication are well told and indeed are unusual in interest and style for a scientific treatise. The reliable microchemical test for lead (p. 14) is one which chemical pathologists have long looked for to supplant the many worthless ones now extant. The chapter on treatment is perhaps too brief for the busy clinician who wishes his science in tabloid form, but a few hours' study of the preceding chapters readily yields the principles of the new acid, alkali or calcium treatment.

W. S.

LACTOBACILLUS ACIDOPHILUS. By NICHOLAS KOPELOFF, PH.D., Associate in Bacteriology, Psychiatric Institute, Ward's Island, N. Y. Pp. 211; 6 illustrations and 113 tables. Baltimore: Williams & Wilkins Company, 1926.

THIS is a monographic review of the work done on Lactobacillus acidophilus, together with major work on Lactobacillus bulgaricus. It includes: The nature of acidophilus therapy, methods used in the preparation of cultures for therapeutic use, the evaluation of the indican test; recommendations concerning dosage and therapeutic

indications and a correlation of clinical records and laboratory findings. Extensive tabulations and full bibliographies are included. The work will be found interesting to those who are impressed by this form of therapy, the benefits of which are still much in doubt.

J. S.

KIDNEY DISEASE FROM THE PHYSICIAN'S VIEWPOINT. By ROLFE FLOYD, M.D., Senior Attending Physician and Pathologist at the Roosevelt Hospital, New York City. Pp. 181. New York: James T. Dougherty, 1926.

To condense into the space of 180 pages the essentials of our knowledge of Bright's disease is the author's attempt. His selection of the authorities whom he quotes for the basis of his description and discussion is excellent. His presentation of the views of these authorities, however, is marred by many inaccuracies and by generalizations which do not appear in such unqualified form in the original sources and which are often unwarranted. Furthermore, the proof reading has been inadequate and errors in typography, spelling and grammar are conspicuous. J. A.

VISUAL FIELD STUDIES. By RALPH I. LLOYD, M.D., F.A.C.S. Pp. 216; 124 illustrations. New York: The Technical Press, 1926. Price, $6.00.

THIS book deals with history of field studies, physiology of the retina, indications for such studies, why the perimetry has fallen into disuse and the advantage of other present-day methods, such as campimeter. He discusses normal fields and blind spots, with a chapter on scotomas and field variations. The diseases in which field studies are essential or of help are briefly considered. Charts present in these affections are given under each heading. The book can be well recommended for its clearness, compactness and practicality. H. S.

MODERN METHODS OF AMPUTATION. By THOMAS G. ORR, A.B., M.D., F.A.C.S., Professor of Surgery, University of Kansas. Pp. 117; 125 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $3.50.

THIS handy monograph on amputation includes only those methods that have proven in the experience of the writer as well as other surgeons to be the practicable and workable ones. The sub-

ject is handled in a very commendable manner and one that should appeal both to students in the undergraduate schools as well as those surgeons who are especially interested in industrial work. The style is pleasing, the subject matter admirably presented and the illustrations profuse and well chosen. The chapter on cinematiplastic amputations, and artificial limbs are especially well chosen and clearly presented. The reviewer heartily recommends the little volume for handy reference. E. E.

BACTERIOLOGY AND APPLIED IMMUNOLOGY FOR NURSES. By R. A. KILDUFFE, A.B., A.M., M.D., Director, Laboratories, Atlantic City Hospital. Pp. 244; 79 illustrations. Milwaukee, Wis.: Bruce Publishing Company, 1926. Price, $2.00.

THIS text is very brief; one might call it a very full outline, but for that very reason it gives the essential facts. The illustrations are diagrammatic and on the whole easily understood. The use of heavy type for the main topics and italics for important words helps quickly to get the facts. Sets of review questions at the end of each chapter and a few suggestions for laboratory work are a practical addition to the text.

This well-bound, concise volume should be of value to both student and teacher in a school for nursing. M. N.

NERVOUS AND MENTAL DISORDERS FROM BIRTH THROUGH ADOLESCENCE. By B. SACHS, M.D., Consulting Neurologist to the Mount Sinai and Montefiore Hospitals, New York; and LOUIS HAUSMAN, M.D., Instructor in Neuroanatomy, Cornell University Medical College. Pp. 861; 110 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $10.00.

THE usual scheme is followed in this very comprehensive work of dividing the subject matter into the following chapters: (1) Introduction, including the anatomy and physiology of the nervous system and methods of examination; (2) organic diseases; (3) functional and toxic diseases; (4) endocrine disorders, vasomotor and trophoneuroses; (5) mental conditions.

One of the most interesting chapters is that on the normal child and normal youth, in which the author airs his well-known and very sound views and for which he himself assumes full responsibility, as he states in the preface. His views about sexuality in infants can be got from the following, on page 720: "Do not stress it, disregard it. Do nothing to develop or to encourage such

feelings, which would not trouble child or parent if the psychoanalyst did not insist on bringing them into the limelight."

This book is one that should interest the neurologist and psychiatrist particularly, but the pediatrist and general practitioner will find therein much of practical interest and value. It is one of the most readable books that has come to the attention of the reviewer. N. W.

THE FURTHER STUDIES ON DECREMENTLESS CONDUCTION. By G. KATO. Pp. 163; 88 illustrations. Tokyo: Nankodo, 1926.

THE author and his collaborators report many additional experiments confirming and extending their earlier work on this subject. The main conclusion is that, in a uniformly narcotized region of of nerve (medullated or nonmedullated) or muscle, the impulse is conducted without "decrement." A study of the threshold to mechanical stimuli near the end of the narcotizing chamber gives direct evidence of the gradient of narcosis postulated in the previous monograph. More data on the spread of electrical stimuli is presented. A subnormal impulse in normal nerve is shown to cause as long a refractory period as a full-sized one. The recovery process in narcotized nerve is shown to be slowed, and the sources of error which led Lucas to the opposite conclusion are pointed out.

H. D.

BOOKS RECEIVED.

A Guide for Diabetics. By WALTER R. CAMPBELL, and MAME T. PORTER. Pp. 259. Baltimore: Williams and Wilkins Company, 1926. Price, $2.50.

Our Doctors. A Novel of Today. By MAURICE DUPLAY. Translated by JOSEPH COLLINS. Pp. 279. New York: Harper and Brother, 1926. Price, $2.00.

The Physiology of the Continuity of Life. By D. NOËL PATON, M.D., B.Sc., LL.D., F.R.S. Pp. 226; 79 illustrations. New York: Macmillan & Co., 1926.

The Human Body. By MARIE CARMICHAEL STOPES, D.Sc., PH.D. Pp. 268; 53 illustrations. New York: G. P. Putnam's Sons, 1926. Price, $2.50.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Ouabaïn: Its Action in Certain Conditions of the Heart.—JAMISON and JONES (*New Orleans Med. and Surg. J.*, 1926, **79**, 173) report on the use of this preparation of strophanthus, ouabaïn, which in 1888 was first prepared by Arnaud. This is a stable, crystalline form of strophanthus, which is invariable in its action. The drug has been used quite extensively in Europe for acute cardiac failure, but apparently has not received very much attention in this country. Vaquez has been particularly struck with the great advantages of the use of this drug. The authors report on a series of 14 patients to whom the drug was given repeatedly, so that there given in all seventy-four injections into the vein. While no definite nor specific cases are reported nor are specific studies on the different cases detailed, nevertheless the authors feel that from their experience ouabaïn is of great value, particularly in the treatment of heart failure associated with aortic regurgitation. Following its use there is a pronounced obliteration of the subjective symptoms and some of the objective symptoms. Their observations are particularly important because this drug offers to the physician a substitute for digitalis, which is notoriously undependable and often valueless in the treatment of syphilitic heart disease.

Ephedrin Therapy in Addison's Disease.—Enthusiastic articles by Chen and Schmidt have led to the fairly widespread use of ephedrin

when the drug has been obtainable. Because of its power to raise blood pressure, it has been believed that it might be of value in numerous conditions associated with hypotension. The similarity in its general action to adrenalin has resulted in the name "vegetable adrenalin" being colloquially applied to it. One of the outstanding clinical conditions in which there is found low blood pressure is Addison's disease, so, naturally, the drug has been tried in this disease in a few isolated cases. However, the Addisonian syndrome is so rare that only a very few clinicopharmaceutical studies have been reported. It has remained for ROWNTREE and BROWN (*Endocrinology*, 1926, **10**, 301) to make use of the enormous clinical material of the Mayo Clinic and to report upon a large series of cases, considering the rarity of the disorder, in which they employed this drug for the relief of the symptoms of Addison's disease. The authors have studied the effect of ephedrin in 14 cases all told, all of which were carefully controlled, and have found that the drug will increase blood pressure and the rate of metabolism, but will cause no significant objective evidence of improvement that may be determined clinically. They feel that the results they have had are disappointing and that this method of treatment is in no way comparable to the Muirhead treatment. Despite the fact that ephedrin apparently has no value in Addison's disease, the authors do feel that the drug may have some value in condition of hypotension associated with nervous exhaustion.

A Method for the Routine Examination of Feces for the Ova of Parasitic Worms and Encysted Amebæ.—It has been definitely shown that very frequently cases of amebiasis are overlooked on account of faulty technique in the examination of the stools. JOHNS (*New Orleans Med. and Surg. J.*, 1926, **79**, 218) says that the present-day methods have several objections, such as the lack of concentration of the specimen through the necessity of using very thin dilutions of the feces, penetration of contrast stain into the cysts within a few minutes, thus rendering them more obscure and the necessity of specialized examination. He has elaborated a method in which watery suspensions of feces are centrifuged and thus very highly concentrated. The exact details of his method will be quoted *verbatim:* "*Method.* Formed or semisolid stools are diluted from ten to fifteen times with water, shaken and strained through two layers of cheesecloth directly into a 12 by 115 mm. ($\frac{1}{2}$ by 4 inches) *round-bottom* tube. Balance tube in centrifuge. (This should be equipped with Cornell shields and should be able to run at least 1500 r. p. m.) Start centrifuge and immediately advance to full speed of 1500 r. p. m. Shut off power within fifteen to twenty seconds after advancing the speed. Pour off the supernatant liquid, resuspend sediment with water and recentrifuge. (Another such washing will frequently clear the sediment still more.) Decant again, leaving a few drops of water to shake up the sediment with. Pour on slide and spread out to where all particles on the slide are easily visible under the low, dry lens and examine as for parasite ova."

SURGERY

UNDER THE CHARGE OF

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Ureteral Stricture.—PEACOCK and HAIN (*Surg., Gynec. and Obst.*, 1926, **43**, 54) state that ureteral stricture is not an uncommon disease. Focal infection and diseases caused by streptococcic infection seem to play some part in the formation of the ureteral stricture. It is more frequent in women than men. Renal colic is frequently caused by ureteral stricture and simulates calculus. Many of the obscure abdominal pains may be traced to ureteral stricture and are relieved by dilatation. A number of abdominal operations have been performed needlessly, as ureteral stricture was undiagnosed and was the cause of the symptoms present. Some strictures are not dilatable and must be subjected to ureterotomy or incision.

Diseases of the Thyroid Gland with Special Reference to Goiter.—WILSON (*Am. J. Surg.*, 1926, **40**, 107) claims that the thyroid gland functions through its active ingredient iodothyroglobulin, a protein-iodin compound. This specific secretion may be likened to a catalytic agent, increasing the rate of formation in the cell of potential energy. Metabolism, therefore, is increased in hyperthyroidism and decreased in myxedema due to decrease of catalytic agent. Of diseases of the thyroid gland, goiter in some form is the anomaly that concerns us most. The simple or colloid goiter presents usually a normal or subnormal metabolic rate. This form of goiter is generally nonsurgical. It usually responds to the administrations of minute doses of iodin or to small doses of thyroid extract. It is very important to differentiate mild exophthalmic goiter from a colloid goiter in a very nervous patient with cardiovascular disturbance. In the adenomatous goiter there are present in the gland one or more encapsulated tumors, which probably have their origin in fetal rests. That the adenoma has no normal thyroid function is shown by the fact that occasionally when one or more adenomas are present myxedema may exist at the same time. In a young person when the adenoma is small and causing no toxic symptoms operation is not demanded. In a patient at or past middle age the adenoma predisposes to malignant changes. Exophthalmic goiter is a constitutional disease characterized by an increased metabolic rate, exophthalmos and hyperplasia of the thyroid. Extreme nervousness and rapid heart action accompany the disease as do sometimes gastrointestinal crises. The exact cause of this condition is not known and various theories have been advanced. It seems that a deficiency of the iodine element might be either a cause or an effect, as it has been shown that the administration of iodin exerts a very favorable influ-

ence over the disease. The treatment is in the main surgical, supplemented by rest in bed and digitalis for cardiac decompensation. Iodin administration, usually in the form of Lugol's solution, combats thyroid crisis. A malignant tumor of the thyroid scarcely if ever develops in a normal thyroid, or possibly 50 per cent give a history of preëxisting goiter. The adenoma is very prone to become malignant carcinoma and seems to be the most frequent, but sarcoma is the most malignant. Surgery offers the best chance for cure of a malignant tumor of the thyroid, provided the growth has not passed beyond the capsule.

The Diagnosis and Treatment of Presurgical Conditions.—MARK (*Therap. Gaz.*, 1926, **50**, 398) claims that it is readily seen that a diagnosis should not be made before sufficient time has been allotted to a thorough examination and reëxamination, calling into play all accessory diagnostic aids, as Roentgen rays, laboratory proceedings, etc. Cardiac reserve must be attended to. Underweight acts as a hazard. It spells lowered resistance and invites infection. On the other hand, patients 35 pounds overweight should be placed on a reduction diet prior to operation. Patients presenting themselves in whom a strong migraine history predominates should have sufficient observation. The importance of premedical treatment in exophthalmic goiter and thyrotoxic adenoma cannot be too strongly stressed. In line of medication the use of Lugol's solution as brought out by Plummer has reduced the mortality markedly as well as allowing for more primary thyroidectomies. Free generous diet and digitalis in cardiac involvement should be stressed. A proper medical regimen in diabetes is essential. The progress made surgically in this condition immediately before and since the introduction of insulin has been marked. The application of insulin in medical preparation of diabetes for surgery is epochal.

Goiter Surgery: Series of Consecutive Thyroidectomies.—MURPHY (*Minnesota Med.*, 1926, **9**, 369) says that the reduction of mortality in surgery of the thyroid gland is one of the noteworthy achievements in the long record of surgical progress. The diseases of the thyroid which may be treated surgically are grouped under the following headings: Diffuse colloid goiter, adenomatous goiter without hyperthyroidism, adenomatous goiter with hyperthyroidism, exophthalmic goiter, thyroiditis and malignancy. The important position of surgery in the treatment of exophthalmic goiter is fully justified by the results obtainable with proper surgical management. The actual operation itself should be regarded as merely one step in the entire procedure and should never be undertaken as an emergency measure. Up to three years ago, successive advances in the treatment of exophthalmic goiter had lowered the mortality to about 3 per cent. But notwithstanding the development of improved methods of anesthesia, general preoperative measures, perfection of operating technique and the employment of graded operative procedures, there still remained uncontrolled the damages of acute postoperative hyperthyroidism, the most frequent cause of death following operative procedures for exophthalmic goiter. Since 1922 this last operative hazard has been overcome through the development by Plummer of a successful method for the prevention and control of the crises of hyperthyroidism.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

The Prophylactic Value of Blood in Convalescents in Measles.—HAAS and BLUM (*J. Am. Med. Assn.*, 1926, **87**, 558) state that it is difficult to procure a sufficient supply of blood of recent convalescents to cope with an epidemic of measles in an institution of fair size. It is practical to bleed recent convalescents in small amounts in order to inject exposed children during epidemic as a prophylactic measure. The plasma of convalescents collected from one to four months after the illness, and stored for four and a half months before injection, protected 51 per cent of the children over a period of three months or more. The plasma of convalescents collected one month after the illness protected 88 per cent of the children for three months or more. Even when plasma of convalescents collected from one to four months after the disease failed to protect, it modified the measles in 100 per cent of the children. It was found that there was very little difference in the protective value of plasma injected from the fourth to the seventh day after exposure. When it was injected after the seventh day it did not protect against or modify the disease. Whole blood in amounts of from 5 to 7 cc. collected up to three months after the disease protected 41 per cent for two months or more. When whole blood collected up to three months after the disease failed to protect it modified the measles, even when it developed two months after the injection. It was found that it was possible but rare to have a relapse of measles within a month. Considering the small amounts of plasma and whole blood that were used, an incidence of 53 per cent in the children who were inoculated as compared to 84 per cent in those who were not inoculated seemed worthy of note. The permanent immunity following the modifications of measles is of benefit in an institution taking care of children. The markedly decreased incidence of bronchopneumonia in the children who received protective inoculation as compared to those who were not inoculated, and the absence of mortality, were important phenomena in this epidemic. The authors feel that convalescent blood is very valuable in institutions harboring infants and young children and in private families where exposure is definitely known.

Blood Changes in Convulsions, Especially in Epilepsy.—WUTH (*Johns Hopkins Hosp. Bull.*, 1926, **38**, 389) noted certain changes in the blood characteristics during convulsion. The various forms of convulsive states in epilepsy and other diseases show marked changes in the cellular and chemical constitution of the blood. He found that there was a polymorphonuclear leukocytosis, an eosinopenia with subsequent oscillation of the curve and a definite decline to the normal level. The lymphocytes vary without any definite rule. Nonprotein

nitrogen, uric acid, creatinin and serum protein show an increase during or shortly after convulsions. Decrease of leukocytes and of serum-protein content combined with increase of the chemical blood constituents in status epilepticus are of prognostic significance. The changes are not always uniform in the same or in different individuals and are not specific for any disease. The changes are not specific for the convulsive reaction, as they may be found as the result of physical exertion To a certain degree, the changes run parallel with the intensity of physical overactivity. The changes described can be regarded as a secondary phenomenon due to convulsions or to physical exertion. As a result of these observations, the writer feels that the theories regarding the causation of epilepsy or the maximum of the convulsive reaction which are based on the changes of the blood constituents will have to be abandoned.

Pyelitis in Infants.—GORTER (*Rev. franç. d. pediat.*, 1926, **2**, 1) observes that there are no characteristic signs of the disease except excessive paleness and swelling of the face. Examination of the urine is the most reliable means of diagnosis. Microörganisms in the urine belong chiefly to the paracolon bacillus group. These bacteria rarely penetrate into the renal pelvis by the urethral route, the infection being chiefly hematogenous. In most of his cases the pyelitis disappeared without leaving any evidence of its presence after one or two weeks. Coëxistence of a congenital malformation in the urinary apparatus seemed to be responsible for the chronic form of the disease. There were no deaths among 53 children over one year of age. The mortality was not more than 10 per cent in the 61 children below this age. Large doses of alkaline citrates seemed to influence favorably the course of the pyelitis. Colon bacillus vaccines helped in certain cases, as well as daily irrigations of the bladder with a 0.1 per cent silver nitrate solution.

Recent Studies of Diabetes in Children.—GEYELIN (*Atlantic Med. J.*, 1926, **29**, 825), in his work reported in this article, makes the observation that following the opinion of Allen upon the harmful effects of high-fat diets on carbohydrate tolerance, he had tried lowering the fat and raising the carbohydrate, although he felt at the time that this procedure would probably require a striking increase in the insulin requirements. Contrary to expectations, when such diets were fed in many of the cases not only were the insulin requirements only slightly increased, but in some instances a five-time increase in the carbohydrate did not require any appreciable change in the amount of insulin given in order to keep the urine sugar free. In several cases in adults the insulin requirements were actually lowered by raising the carbohydrate and lowering the fat intake. This procedure has several advantages over the accepted form of diet in insulin-treated cases. A more normal proportion between carbohydrate, proteid and fat is obtained. This is also more agreeable to the patient, and in the case of children it has proved very successful in diminishing the frequency of dietary infractions. The higher carbohydrate diets have also tended to diminish the frequency of insulin reactions. They have the tendency to keep the patient more constantly sugar free and may play

some part in decreasing the risk of coma. His results, as tabulated, tend to show that the number of grams of carbohydrate oxidized per unit of insulin is in general higher when the carbohydrate is raised and the fat is diminished. The conclusion, therefore, seems evident that excess fat in the diet tends in some way to diminish the effectiveness of insulin in many cases of diabetes. Other authors have given experimental evidence tending to support the conclusion that insulin is more effective in the presence of high-carbohydrate and low-fat diets than it is in the presence of high fat and low carbohydrate. The author continued the experimental work on rats and shows that groups of rats fed on diets high in fat with no carbohydrate were more resistant to insulin effects than were animals fed on normal diets. These were still more resistant to insulin effects than were animals fed on diets high in carbohydrate and free from fat. The 51 children suffering from diabetes who were under the insulin treatment for varying period were none able to discontinue insulin and they appeared to be nearly as dependent upon it as they were three years ago, but nevertheless it is evident the insulin requirements have been somewhat lowered. Even in those cases where this does not seem true it must be remembered that these individuals are actively growing and it must be reasonably expected with the increase in total mass and greater total metabolic activity that a progressive increase of insulin would be required. In no case was the increase in the amount of insulin required to keep the urine sugar free in proportion with the increase of body weight. As a result of these observations, it would seem that the progress of diabetic children offers much encouragement as to the eventual outcome. A case of another author is cited in which after continuous use of insulin for two years the patient was accidentally killed and the autopsy revealed definite evidence of regeneration of the islands of Langerhans. It must be remembered that the insulin-treated child is still a potentially severe diabetic, but on the whole progress in the majority of instance has resulted, and mental and physical development have taken place in a qualitative manner.

OBSTETRICS

UNDER THE CHARGE OF

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Conduct of Labor after Cesarean Section.—GLADDEN (*Am. J. Obst. and Gynec.*, 1926, **11**, 642) believes the dictum "once a Cesarean, always a Cesarean" is highly erroneous. In earlier years the rupture of

Cesarean scars in subsequent pregnancies was high, due to ineffective methods of suturing then in vogue. Since the adoption of Sanger's method, or suturing in tiers, the incidence of rupture has greatly decreased. If the closure of the uterine incision is done correctly, and there is no subsequent infection, the scar will be able to withstand the strain of pregnancy and labor. Experiments have shown that rupture usually took place in the muscle or else began in the scar and extended through the musculature at the side of the scar. The author studied a series of 21 cases of subsequent pregnancies following Cesarean section due to other causes than the absolute one of contracted pelvis. Six were delivered by repeated Cesarean section, with 2 deaths, and 15 were allowed to go into labor, 3 of which ruptured with fatal termination in 2 cases. Two of the cases which ruptured were admitted after the rupture had taken place and had not been carefully supervised during pregnancy and labor. The other 12 were delivered by vaginal route by breech extraction, or mid or low forceps. Of these, 12 patients had delivered five times by the natural route since her first delivery by Cesarean section. Unless the first operation was done for an absolute cause, as contracted pelvis, the author believes the risk is less if the patient, properly supervised in a hospital, is delivered vaginally. The incidence of ruptured Cesarean scars is reported as being from 2 to 4 per cent, while the mortality following Cesarean section averages 10 per cent or more.

Pregnancy, Parturition and Health after Surgical Replacement of the Uterus: A Retrospect.—In this article REYES (*Surg., Gynec. and Obst.*, 1926, **43**, 317) has followed up carefully a series of selected cases. The patients chosen were not favorable ones, which might show the best end results, but were those which included patients during the child-bearing period who for obvious reasons needed a correction of their uterine displacement and who presented no other lesions or had no other operation performed upon them. Approximately 50 per cent of the cases were followed up. The results were most gratifying, in that the operation of surgical replacement of the uterus did not appear to affect unfavorable pregnancy, parturition and their future health. The pathologic lesions found in these cases at operation included laceration of the perineum, stenoses of the cervix, hypertrophies of the cervix, endocervicitis. There was a uniformly smaller percentage of lesions among the patients in the positive than in the negative group.

Induction of Labor.—BAULD (*Canadian Med. Assn. J.*, 1926, **16**, 677) states that indication for induction of labor falls broadly into four main groups: (1) Those in which there is a definite disproportion between the maternal tissues and the fetus; (2) those in which induction is indicated on account of toxemia; (3) those in which ante partum hemorrhage is the leading factor; (4) where induction is indicated by cardiac, pulmonary or other extraneous conditions. Under the first therapeusis is alone used, with the object of sensitizing unstriped muscle, and including subcutaneous injection of pituitary extract, giving the dangers and the frequent failures. The rupture of membranes falls under the second group and is purely mechanical, as is likewise so in Group 3, in which bougie and packing are the mechanical

irritating factors. Under the fourth group the hydrostatic bag is used, which is the most active and rapid method of effecting delivery, while the bougie and pack is uncertain and slow. The rupture of membranes has a specific indication with hemorrhage and in hydramnios. The therapeutic measure, medicinal only, has often a successful outcome, and may be used in selected cases and in certain modified forms.

GYNECOLOGY

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Milk Injections for Pelvic Infections.—For some time GELLHORN (*New Orleans Med. and Surg. J.*, 1926, **78**, 557) has been an enthusiastic supporter of the treatment of pelvic infections by means of milk injections. In explanation of the rationale of this method, he states that nonspecific therapy of inflammatory diseases consists of the subcutaneous, intravenous or intramuscular injections of protein substances which are in no wise related to the causative bacteria. Protein substances, thus introduced "parenterally," have the faculty of activating the protoplasm of all cells in the body and particularly of those cells which are engaged in warfare against the invading microörganisms. This plasma activation serves to mobilize the natural defensive powers of the body and to overcome the infection. Of the various protein substances recommended, milk is most easily available and at the same time highly efficacious. Ordinary household milk is rendered fat free by centrifugation and boiled in test tubes in a water bath for ten minutes in such manner that the test tubes do not touch the bottom of the vessel. By first sterilizing the centrifuge tubes and test tubes, the probability of imperfect sterilization of the milk is averted. The milk is then drawn through a long needle into a sterile syringe and is injected into the upper portion of the buttocks under the usual antiseptic precautions. Focal irritation denotes insufficient disinfection of the skin. If the injection is made slowly and through a long, thin and sharp needle it should be practically painless. Absorption is speedy and in thousands of injections the author has never observed an abscess. The initial dose is 5 cc.; the standard dose is 10 cc., which is reached with the second or third injection and then maintained throughout the course of treatment. In very feeble patients the first dose may be as low as 3 cc. and very cautiously increased. The interval between injections is from two to three days, guided largely by the clinical aspect of the case and the leukocyte count. When the latter has

receded sufficiently from its peak new stimulation is in order, but the *first* injection is given no matter how high the count is. The "general" reaction sets in about six hours after injection and is usually slight. Gonorrheal infection of the tubes and Bartholin's glands is most often amenable to protein therapy; in other locations of the infection the therapeutic result is less conspicuous. Nongonorrheal inflammations of the genital tract are also often cured by this treatment. The treatment is contraindicated in cardiac decompensation, diabetes, alcoholism and perhaps pregnancy. It should be used cautiously, if at all, in cases of quiescent pulmonary tuberculosis, epilepsy or where there is a history of hypersensitiveness, such as serum sickness, asthma, urticaria or angioneurotic edema. In an advanced stage of infection protein stimulation is unable to revive hopelessly damaged cells, and if applied in an utterly exhausted patient it may even hasten the end. The method is still in its early stages and is capable of further development.

Reconstruction of the Urethra.—In considering the problem of the reconstruction of urethral defects complicating vesicovaginal fistula, LEHOCZKY-SEMMELWEIS (*Zentralbl. f. Gynäk.*, 1926, **50**, 1175) states that there are two factors to be considered: The first, which is the easier one to solve, is the replacement of the urethra; the other, which is more difficult, is the resumption of the function of the wounded sphincter muscle. In the case which he cites a girl, aged fifteen years, came to his clinic on account of leakage of urine as the result of a wound caused by a fracture of the pelvic bones. On examination, it was found that the urethra was completely gone and in its place there were many scar tissue adhesions complicating a cystocele of the anterior vaginal wall about the size of a pigeon's egg through which there was an opening into the bladder large enough to admit a finger. Without much hope for cure, he freshened the edges of the fistula and unite the bladder wall with catgut without entering the mucous membrane of the bladder. The vaginal wall was then closed with silk sutures, narrowing the opening of the fistula to such an extent that only a very thin catheter could pass. A retention catheter was then inserted and allowed to remain eleven days and good healing occurred. A year and a half later she returned to the clinic stating that she was much improved but could not hold her water when she did hard work. The anterior vaginal wall was very much prolapsed and he felt that if this could be elevated her condition might be further improved. He, therefore decided to reconstruct a new urethra, and for this purpose he removed a strip of the vaginal mucous membrane, $\frac{1}{2}$ cm. broad, from the cystocele on each side of the opening into the bladder extending from the lowest point of the cystocele up to the clitoris. Between these two denuded strips a flap of mucous membrane about as broad as a finger was allowed to remain. With interrupted catgut sutures, the upper and lower parts of the denudations were united, thus forming a new urethra and at the same time elevating the prolapsed vaginal wall up to the clitoris by means of which the external opening of the fistula was made to lie $1\frac{1}{2}$ cm. higher. The retention catheter was then inserted through the new urethra and the patient made a good convalescence. Following this operation, the patient was able to hold the urine for a longer time, and she seemed to have some sphincter control.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Tuberculosis of the Eye.—WEEKS (*Am. J. Ophth.*, 1926, **9**, 243) finds tuberculosis of the eyelids externally as lupus erythematosus, lupus vulgaris, and cold abscess. Tuberculosis of the conjunctiva is present in at least four forms; lupus vulgaris, lupus erythematosus, acute miliary tuberculosis, tuberculosis resulting in a thickening of the palpebral conjunctiva principally. In the cornea tuberculosis shows a marked resemblance to the socalled phlyctenular keratitis in some cases. Tuberculosis of the iris may be miliary or conglobate. The nodules appear in the major and minor zones of the iris, having no selective tendency for either, in contradistinction to papillary syphilides which always appear in the minor zone of the iris. Diagnosis of tuberculosis of the ciliary body and choroid must often depend upon tuberculin tests though in both miliary and conglobate forms characteristic appearances can often be made out with the ophthalmoscope. A differential diagnosis between tubercle and leukosarcoma, or glioma, should be made if the mass is small. Since it is often impossible to make a diagnosis of ocular tuberculosis by means of the microscope, ophthalmoscope or history of the case, it is necessary to resort to tuberculin reaction tests. Tests that produce a reaction at the site (focal infection) of the eye lesion are the only positive tests. He advises the use of "T.O." for diagnostic as well as therapeutic purposes. For diagnostic tests in adults he injects subcutaneously "T.O." 0.5 mg. If no reaction occurs in three days 2 mg. may be given. If no reaction follows injection of 2 mg. a third dose of 3 to 4 mg. may be injected. For therapeutic use the initial dose should be small, "T.O." 1/200 to 6/100 mg. and doubled at each injection until some signs of systemic reaction are induced.

A Case of Metastatic Intraocular Mycosis.—VERHOEFF (*Arch. Ophth.*, 1926, **55**, 225) studied a fatal case of unilateral intraocular mycosis, evidently metastatic from some systemic focus, in which there was clinical evidence of involvement of the liver and endocardium. The character of the disease was disclosed by pathologic examination of an eye which had been removed for metastatic purulent endophthalmitis. Physical findings were chronic mitral disease, slight enlargement of the liver and malnutrition. The eye was enucleated June 11, 1925. The patient died October 10, 1925, "with symptoms of paralysis" as stated by his wife. The organisms found formed granules and clubs resembling those of actinomycosis. The organism differed from actinomycetes in that the filaments which composed the granules were more delicate, unbranched, and gram negative. They were also nonacid fast. In spite of the treatment with potassium iodid the patient died in

about five months after the onset of the first symptoms. It is suggested that such cases, but of a milder type and without ocular involvement, may not infrequently occur, and escape recognition.

Edematous Anthrax of the Face Resulting in Meningitis.—KRAUSS and SPIKES (*Am. J. Ophth.*, 1926, **9**, 337) were consulted by a man, aged thirty-five years, a piecer of yarns, who had a small swelling, thought to be a sty, on the right upper eyelid of two days' duration. There was an intense swelling of both lids of the right eye. No external lesion of any kind could be found to account for the edema. Two days later he had a convulsion and was hospitalized. The swelling rapidly increased, was hard, brawny, with a rather sharply defined edge. Temperature was 102°. White blood cells 10,800. Wassermann reaction negative; blood culture negative. He became comatose, the neck spastic, hands and fingers athetoid. Smear of spinal fluid showed very many pus cells and anthrax bacilli. He died of pulmonary edema thirty-six hours after admission to the hospital. Autopsy showed suppurative meningitis due to anthrax bacilli.

A Study of the Influence of Protein Therapy on Experimental Staphylococcus Infection of the Cornea of the Rabbits.—KEY (*Surg., Gynec. and Obst.*, 1926, **42**, 473) injected into the corneæ of rabbits a dilute emulsion containing staphylococci grown on artificial media for twenty-four hours before inoculation. He used dilutions of this emulsion that gave quite uniformly corneal lesions, then soon after the injections into the cornea, he injected into the abdominal muscles the foreign protein. The protein used were antidiphtheritic serum, concentrated horse serum, typhoid vaccine and sterile milk. In almost every experiment in which any difference could be noted, the animal which received the protein injection showed the least corneal reaction to the infecting microörganism. No important difference, however, between the effec- of antidiphtheritic serum, concentrated horse serum, and typhoid vaccine upon the infection could be observed in any of the experiments.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Presence of Diphtheria Bacilli in the Nasal Cavity of the Newly Born.—The occurrence of Bacillus diphtheriæ in the nasal cavities of the newly born ranges among various observers from 2.5 to 84 per cent. AMBERG (*Minn. Med.*, 1926, **9**, 341) cultured the nares of 421 newly born infants. In 182 cases only 1 culture was taken; in 239, 2 cultures; in 16, several cultures. The study extended over a period of two years, the babies being studied at the Mayo Clinic. The cultures

were planted on Loeffler's blood serum. Diphtheria bacill were found in 19 instances, or 4.5 per cent. Usually staphylococci were encountered in the cultures; more rarely streptococci. A small number of cases yielded sterile cultures. The bacilli in the nasal cavities were as a rule avirulent, so that the relative frequent occurrence of these microorganisms in the nares of newly born infants must be distinguished from diphtheria of the newly born.

Mastoiditis without Apparent Otitis Media.—The infrequency of mastoiditis without apparent otitis media is shown by the fact that Hempstead, in 1923, was able to collect 50 cases from the literature adding 3 of his own. More recently HANSEL (*Arch. Otolaryngol.*, 1926, **3**, 433) has found 7 cases reported since Hempstead's review, and gives the clinical data of 2 additional cases which came to his personal attention. Both of these occurred in females, aged forty-five and eleven years, respectively. Both gave a history of a cold in the head at the onset, and at that time there had been "undoubtedly" an otitis media. At the time of operation, however, there was no evidence of otitis media. The mastoid antrum in each case was small and the aditus ad antrum was narrow. Streptococcus hemolyticus was the causative microörganism in both instances. The author discusses the various types of involvement and reaction of acute otitis media and mastoiditis, differentiating between latent suppurative otitis media and without apparent otitis media. He stresses the presence of aural discharge after paracentesis tympani in the former and its absence in the latter. He also emphasizes the fact that the most logical advent of infection in "primary" mastoiditis is by way of the Eustachian tube to the tympanic cavity, thence to the aditus ad antrum which is usually very narrow and becomes obstructed early by the inflammatory exudate. He believes that it is altogether likely that in the early stages of the disease there is an inflammatory process by way of the middle ear, which later subsides when the aditus is occluded. "It would seem," he says, "that this type of mastoid disease is dependent on the anatomic peculiarities which exist in the mastoid process, rather than due to some specific organism," although he recognizes the possibility of a former otitis media and mastoiditis causing a narrowing of these pathways. Later HEMPSTEAD (*Ann. Otol., Rhinol. and Laryngol.*, 1926, **35**, 517) reports 6 cases of "definite mastoiditis in which the middle ear was definitely not affected." Since 3 of these cases occurred prior to 1923, it is possible that they are included in Hansel's references. The author, too, calls attention to the low incidence of this condition, as compared with more than 500 cases in which the middle ear was affected during the same period. He cautions that the term "primary mastoiditis" is misleading, since the infection must be primary in the mastoid cells, and not secondary to an inflammation of the middle ear that has cleared up—a point also made by Hansel. Of the 6 cases, 5 were males. The ages ranged from fourteen to seventy-five years. Four of the cases gave a history indicating an antecedent otitis media without symptoms. The predominance of Streptococcus mucosus (pneumococcus, Type III) in these cases is given as a warning of the danger in this type of infection, and should put one on their guard when this bacterium is found in an acutely discharging ear. The author also

mentions the finding of the small aditus ad antrum in some of his cases. WEINSTEIN (*Laryngoscope*, 1926, **36**, 320), in recounting a case of "acute mastoiditis without apparent middle-ear symptoms" in a girl baby, aged fourteen months, also reviews the literature. The first indication of mastoid disease was a left-sided postauricular swelling. Both ear drums appeared to be healthy and myringotomy on the left side yielded no pus. At operation a subperiosteal abscess was found. This led into a necrosed mastoid process by a fistulous opening through the cortex. The antrum was filled with granulation tissue and pus, blocking firmly the aditus ad antrum. A nonhemolytic streptococcus was recovered on culture. The author believes that the infection in these cases extends from the nasopharynx, by way of the Eustachian tube, through the tympanum to the mastoid. The accompanying engorgement of the mucosa of the antrum and aditus is at times sufficient to block the latter and limit the infection to the mastoid, while the tympanic cavity symptoms may be so mild as to escape notice or be apparently absent.

The Chemotherapy and Serum Therapy of Pneumococcus and Streptococcus Meningitis: I. A Résumé of the Present Status of the Treatment of Septic Meningitis, with the Recommendation of a Method.—KOLMER (*Arch. Otolaryngol.*, 1926, **3**, 481), assisted by Miss Rule and Mr. Madden, details the results of numerous experiments observed in the chemotherapy and serum therapy of pneumococcus and streptococcus meningitis, employing as the animals for experimentation rabbits, white rats, guinea pigs and dogs. The experimental meningitis was produced by injecting intracisternally into the etherized animal (usually dogs) 0.1 cc. of an approximately 1 to 5 dilution of twenty-four-hour brain-hormone broth culture of highly virulent hemolytic streptococci per kilogram of weight, or 0.1 cc. of a 1 to 50 to 1 to 100 dilution of a similar culture of pneumococcus per kilogram. Untreated controls were used in every experiment. It was found that the daily intraspinal, intracisternal or intraventricular injection of ethylhydrocuprein hydrochloride in dose of 0.0002 gm. per kilogram had no appreciable curative effects in the treatment of acute experimental pneumococcus meningitis of dogs; no better results were secured by combining these routes of administration with the intravenous or intramuscular injections of the compounds; combined treatment with antipneumococcus serum and ethylhydrocuprein did not improve the results, although some improvement was noted in combined treatment with pneumococcus antibody solution; especially good results were secured by lavage from the ventricles to the cisterna magna, followed by intraventricular and intracisternal injections of the drug, but lavage alone yielded similar results. Mercurochrome, given in proper dosage intravenously, subdurally or intracisternally, was ineffective in the treatment of staphylococcus meningitis of rabbits and streptococcus and pneumococcus meningitis of dogs. Similarly, gentian violet, neutral acriflavin and rivanol showed no beneficial effects on the course of the experimental meningitis of dogs. Polyvalent antistreptococcus serum administered by intramuscular, intravenous, intracisternal and intraventricular injection failed to influence appreciably the course and mortality of experimental hemolytic streptococcus men-

ingitis in dogs, nor did Type I antipneumococcus serum influence appreciably the course and mortality of experimental Type I pneumococcus meningitis of dogs. The author emphasizes that lavage of one or both of the lateral ventricles to the cisterna magna has proved effective in the treatment of severe experimental streptococcus and pneumococcus meningitis of dogs. This method, which he recommends, may be performed by using warm saline or Ringer's solution, or by combining this with the administration of antibody solution by subthecal injection in the treatment of pneumococcus meningitis or by the injection of gentian violet in the treatment of streptococcus meningitis. He further states that lavage from the cisterna to the lumbar region of the spinal cord may be done at the same time, although he is convinced that septic meningitis kills from the cisterna upward rather than by spinal meningitis.

Some of the Problems of the Hard-of-hearing and their Solution.—Within the past two decades great strides have been made in the management of the deaf, but HAYS (*Ann. Otol., Rhinol. and Laryngol.*, 1926, **35**, 564) regrets to say that we are far from that millenium where we can promise that we can cure deafness. This, he attributes to the negligence of the patient on the one hand and the impossibility of definitely interpreting the pathologic condition causing the aural defect on the other. The greatest encouragement has been found in the interpretation of the causes of deafness and in the management of the average case which is amenable to treatment. The time-worn employment of aural inflation by catheter or by Politzerization has practically been discarded and the intelligent otologist will not be satisfied until he has made a thorough hearing test, has examined for the causes of the aural lesion and has treated the pathologic condition as he has found it. Great aid has been given by the use of the nasopharyngoscope and the auroscope. He feels that "The one factor which will count for more than anything else in the advancement of our knowledge of this subject is the awakening of interest in it on the part of the otologists." After an earnest and fair discussion of the relation of the various cults to deaf persons, he treats of the influence of the League for the Hard-of-Hearing in correcting many of the present-day evils. He stresses the field of preventive measures, mentioning that about 3 per cent of school children are suffering from ear conditions which interfere with their school work, that half of these cases are due to suppurative lesions and the other half to catarrhal otitis, that many of these children should have attention to their noses and throats, that improper blowing of the nose has caused relaxed ear drums in many of them, that a majority of the suppurations can be arrested by proper treatment without a radical mastoid operation and that 80 per cent of the children with catarrhal conditions can be improved or cured by simple Politzerization. In conclusion, he says that the advances that have been made in the treatment of the deaf are: (1) The attitude of the otologist toward his deaf patient has changed; (2) more interest is taken in the prevention of deafness; (3) psychologic treatment is of the utmost importance; (4) the elimination of the charlatan will depend on the success of a campaign of education against him; (5) the lay organizations for the deaf are helping a great deal in solving the problem of the deaf.

RADIOLOGY

UNDER THE CHARGE OF

ASSISTED BY

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The Roentgenologic Diagnosis of Gastrojejunal Ulcer.—MOORE and MARQUIS (*Am. J. Roent. and Rad. Ther.*, 1925, **14**, 432), basing their report on 200 cases of gastrojejunal ulcer seen at the Mayo Clinic, found an incidence of 2.3 per cent following gastroenterostomy, 93 per cent in men, with an average interval of six weeks to twenty-one years after operation. They believe the cause to be a combination of factors rather than any one. The ulcer is usually single and smaller than the ordinary peptic ulcer, but may be multiple, or large enough to resemble carcinoma. No carcinoma, however, has been found. In some conditions there may be only a marked inflammation without ulcer, but the penetrating type is the most common and is usually situated in the suture line. In this series 17 cases of perforation with gastrocolic fistula were encountered. Eusterman notes that the symptoms of ulcer appear early and are about the same as previous to operation, but that the pain is lower and more to the left. Periodicity is uncommon and there is no food or alkali relief. The authors emphasize the importance of keeping in mind the normal appearance of an anastomosis. The stoma should be not less than 6.25 cm. in length and placed in the most dependent part of the stomach. The flow into the jejunum may be constant or in spurts. There should be no retention in the stomach or adjacent small bowel and the stomach is regular in contour except for slight dimpling at the anastomosis; it is pliant, and the rugæ are normal save for slight convergence and coarseness at the opening. The authors call attention to Carman's classification of the signs of gastrojejunal ulcer into two groups: first, indirect or those indicating abnormality in the anastomosed stomach, and secondly, the direct, or those pointing to the seat of the trouble. They call attention to the importance of knowing what type of surgery was done, as an irregular or faulty anastomosis may give symptoms simulating ulcer. One of the most important indirect signs is a large stomach, indicating retention. The direct signs are best elicited by careful palpation and manipulation of the stoma and surrounding areas, turning the patient to gain different angles of view. The authors have found that deformity of the stoma appears as a retraction and drawing up of the greater curvature, which may be due to spasm or cicatricial contraction. One must palpate carefully for the possibility of demonstrating the crater of the ulcer, which should appear as a small localized area of greater density due to the retained barium. Perforation of gastrojejunal ulcer into the colon is best demonstrated by a barium enema. Herniation

of the jejunal loop through the gastrocolic mesentery opening may occur and give symptoms of ulcer, but this is characterized by early onset after operation, marked obstruction, extreme dilatation of the jejunal limbs and narrowing some distance from the stoma.

The Reliability of the Niche in the Diagnosis of Gastric Ulcer.—As the diagnostic reliability of the niche has occasionally been criticized adversely, HAUDEK (*Fortschr. a. d. Geb. d. Roent.*, 1925, **33**, 651) defends it with energy. At the outset he states that the sign is entirely reliable if the complete sign-complex is present and if the niche is situated on the pars media. Taking up the cases reported in which a supposed niche led to an erroneous diagnosis, he argues that in every instance there was an indefensible error either of observation or of interpretation. In Kurtzahn's case Haudek insists than an ulcer was present and the surgeon merely failed to find it. A cancer in the head of the pancreas producing a fold in the stomach caused the mistake in 1 case; in another a small calcification in a pancreatic tumor was misinterpreted as a niche, and in a third the duodenojejunal flexure crossing the lesser curvature caused the semblance of a niche. Other simulants mentioned by the author include stone in the left kidney, gastric diverticula, the fold on the lesser curvature between two peristaltic waves, and ulcerating cancer. Gastric diverticula have their typical site in the cardia. The niche of benign ulcer is wholly or partly outside the gastric profile, is rounded, has a narrow neck, and the rugæ radiate from it; that of ulcerating primary cancer is within the gastric profile, is irregular and broad based, and the rugæ are irregular. Distinction between a benign ulcer and one which has undergone secondary malignant degeneration is difficult. Large size of the niche is one indication of malignancy, and the slightest deviation from the typical signs of ulcer must be taken as a warning signal of possible malignancy.

Roentgen Treatment of Spontaneous Posttraumatic and Postoperative Coccus Infections and Suppurations.—Observations that Whitlow's and other coccus infections of limited extent heal with remarkable rapidity after Roentgen treatment have appeared in the literature over the last twenty years. HOLZKNECHT (*Am. J. Roentgenol. and Rad. Therap.*, 1926, **15**, 332) predicts, as a result of extensive research by several observers, a radical change in the therapy of acute and subacute coccus inflammations through the introduction of Roentgen therapy. The experiences of himself and others has been that 50 to 90 per cent of even the severest cases recover almost immediately after irradiation, or else run a very much shorter course. The correct dose is an unusually small one, 1 to 2H, filtered through 0.5 mm. zinc, brass or copper. Larger doses apparently impair in some manner the extraordinarily sensitive optimal conditions for healing. Radiation should be administered early, before surgical intervention. Many hundred cases have been treated; two-thirds were favorably influenced; in one-third the processes were aborted and receded by crisis; in one-third there was rapid recovery by lysis. Infections of the nasal sinuses and some infections in other localities were not appreciably influenced.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Parkinsonism following Carbon Monoxid Poisoning.—In his report of a case GRINKER (*J. Nerv. and Ment. Dis.*, 1926, **64**, 18) believes that in carbon monoxid poisoning there is pallidial localization, resulting from an initial vascular paralysis, followed by an asphyxia of the structure, due to a poor capillary supply. The bilateral involvement of the pallidium probably produces the rigidity and akinesis noted. The white matter presents degenerative changes of a diffuse parenchymatous lesion without softening or vascular reaction. This is best termed myelinopathy and is probably responsible for the psychic state noted.

Blood Calcium and Phosphorus in Personality Disorders.—In a study of calcium determinations on 88 cases and phosphorous determination in 68 cases, HENRY and EHELING (*Arch. Neurol. and Psychiat.*, 1926, **16**, 48) find that while the content of these in the blood in personality disorders is within normal limits, there is a relative increase in manic states and a relative decrease in depressions, hence phosphorous and calcium therapy in the latter. In dementia precox there is no difference in content between acute and chronic cases, although the calcium content is lowest in the catatonic type. The ultraviolet ray produced no effect on the calcium and phosphorous content in personality disorders.

Action-Tremor.—DE JONG (*J. Nerv. and Ment. Dis.*, 1926, **64**, 1) formulates "tremor as an extrapyramidal clonus," the "normal preventive inhibitory mechanism" being decreased under pathologic conditions. He believes that all "striatal tremors, including rest tremors are action tremors," the difference being quantitative rather than qualitative. Hence, rest tremor is probably a very heavy action tremor. The action tremor, he believes, is quite different from the intention tremor, and the two should not be confused. The former is static and locomotorial, results from any psychic or physical activity, is regular, usually involving a circumscript group of muscles, whereas the latter is locomotorial, comes at the end of a movement; is rhythmic but unequal in its oscillations, the whole limb moving around an equilibrium position. The frequency of the action tremor was greater in the cases studied than was that of the intention tremor.

Intracranial Aneurysms.—SANDS (*J. Nerv. and Ment. Dis.*, 1926, **64**, 12) reports a case of intracranial aneurysm, the symptoms of which fitted Symonds' classification: (*a*) Neighborhood symptoms due to the pressure; (*b*) those due to the underlying disease; (*c*) those due to presence of the aneurysm—leakage and so forth. He believes that intracranial aneurysm should be considered in cases showing signs of pressure on brain tissue, especially if there is bloody spinal fluid, cervical rigidity, positive Kernig and cranial nerve lesions. The intermittency of the symptoms is also characteristic.

Loss of Weight: Its Importance as an Early Symptom in General Paralysis.—BUNKER (*Arch. Neurol. and Psychiat.*, 1926, **16**, 63), in a study of 74 male cases of general paralysis, stated that 50 per cent showed a loss of weight prior to the development of mental symptoms and one-fourth of these also gave a history of bulimia. Thirty per cent showed loss of weight as the earliest deviation from the normal. In 20 per cent of cases this was a later manifestation. No loss of weight with bulimia was noted in 10 per cent. These findings may have some bearing on the therapeutic response of the patient.

A Study of Subject Matter and Motivation of Children's Dreams.—BLANCHARD (*J. Abnormal and Social Psychol.*, 1926, **21**, 24), in a study of 300 children under eighteen years of age in a somewhat selected group, found 82 per cent were able to recall fragments of their dreams. Fifty per cent of these 300 children were referred for clinical diagnosis because of behavior disorders and 25 per cent because of undesirable personality traits. Fifteen per cent of the dreams reported were concerned with parents. Fourteen and a half per cent were about animals which the author believes can most logically be interpreted in the light of the child's everyday experiences. Thirteen per cent of dreams were "fear dreams." The remaining dreams were grouped under various headings, such as death, sex, riches, etc. It seems possible that a child's dreams may be a "short cut to an understanding of some of the more subtle phases of the child's feelings and attitudes in respect to himself and his situation."

The Levulose Tolerance Test in Paralysis Agitans.—In a study of 18 cases of idiopathic paralysis agitans. HURST (*J. Neurol. and Psychopath.*, 1926, **6**, 291) believes that the hyperglycemia frequently noted in these cases is probably the result of a coincident vascular disease rather than of the nervous affection. The levulose tolerance test as performed on this series of cases did not show any evidence of liver deficiency.

Weight of the Heart in Dementia Precox.—REED (*The State Hosp. Quart.*, 1926, **11**, 377) in a study of the findings of 318 autopsies on psychotic patients, of which 124 were dementia precox, found that it was where there was no physical cause for the alteration in the size of the heart the weight was the same as in cases without dementia precox. Also in contrast to the work of Lewis, this author believes that the dementia precox heart does not lack the power to hypertrophy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Effect of Sanocrysin on Tubercle Bacillus in Vitro.—In a brief historic review of the use of gold salts in the therapy of tuberculosis, SWEANY and WASICK (*Am. Rev. Tuberc.*, 1925, **12**, 316) point to Koch's demonstration of the inhibitive action of potassium aurocyanide on broth cultures of the bacillus in dilutions of 1 to 2,000,000. This concentration was found ineffective *in vivo*, and the serum globulin was held responsible in preventing the diffusion of the salt. Mollgaard brought out his sanocrysin, claiming that it fulfilled the requirements of being: (1) Water-soluble to penetrate tuberculous tissue; (2) diffusible to pass the waxy covering of the bacillus; (3) slowly decomposable, without forming free gold and toxic products. The authors aimed in their reported experiments to increase the understanding of the action of this drug sodium—aurothiosulphate *in vitro*. The figures show that agar cultures of the bacillus were inhibited in dilutions of 1 to 1,000,000 to 1 to 500,000, and broth cultures were twice as susceptible. The bactericidal effects were nonoperative in concentrations as high as 1 to 2000 and after a three months' exposure, as proven by guinea-pig inoculation. It was found that the granular forms of the bacillus were acted upon by the salt and, as this type is more characteristic of the chronic stage of the disease, the therapeutic use seems indicated as not for the acute cases. Also as the action is not bactericidal, the theory of tuberculin shock associated with the use of sanocrysin seems unfounded and the employment of antiserum unnecessary.

Varying Degrees of Malignancy in Cancer of the Breast.—Following the work of MacCarty and later Broders, who attempted on histologic findings to classify cancers of the lip and skin into varying degrees of malignancy, GREENOUGH (*J. Cancer Res.*, 1925, **9**, 453) has gone over a series of 73 breast carcinomata and grouped them histologically into three groups: Low malignancy, 19 cases: 13 cures, 68 per cent; medium malignancy, 33 cases: 11 cures, 33 per cent; high malignancy, 21 cases: 0 cures, 0 per cent. The data as to cures was obtained from clinical investigations. He found the degree of differentiation as shown by the arrangement of cells around an open gland lumen (adenocarcinoma); the degree of secretory activity of cell protoplasm as seen by vacuoles and droplets of mucoid material; the uniformity of size of cells and nuclei and the absence or paucity of hyperchromatic changes and mitotic figures, all varied directly with the degree of malignancy. High malignancy was shown by cells and nuclei of irregular size and

shape, without secretory function, and arranged in solid columns large and small, together with numerous irregular mitoses and hyperchromatism. A tumor of adenomatous arrangement with uniform cells and nuclei and few mitoses indicates low malignancy. A high degree of round-cell infiltration seems to indicate a considerable degree of degeneration rather than any resistance on the part of the individual to the cancer growth. Hyalinization of the stroma was rather a factor of the age or previous condition of the mammary tissue than an indication of active resistance to the tumor growth.

The Persistence of the Glomerular Circulation following Occlusion of the Renal Vein of One Kidney in the Cat.—With a view of determining experimentally whether any characteristic changes followed venous obstruction of the kidney that might be used as an explanation of "symmetrical necrosis of the kidney" so often reported as associated with pregnancy, ZECKWER (*Am. J. Path.*, 1926, **2**, 57) ligated and excised the left renal vein in a series of cats. The animals were killed at varying intervals of time. In brief, she found this resulted in congestion and edema followed by degeneration of the tubules. A clearly defined zone of necrosis in the periphery of the cortex occurred, beneath which was a zone in which the tubules were degenerating and the glomeruli remained intact. Later stages showed a widespread necrosis of the tubules while many glomeruli persisted. The extensive destruction of the tubules resulted in extreme atrophy of the organ which then seemed to be made up almost entirely of glomeruli and capillaries. Injection of the capillary circulation with Berlin blue demonstrated the course of the blood from the main renal artery through afferent glomerular arterioles, then through postglomerular capillaries to the external anastomosing channels. Tuffier and Lejars had previously noted these extra renal anastomoses to be capsular renal, capsular mesenteric, capsular suprarenal, capsular spermatic and capsular lumbar. Apparently this independence of blood supply of the glomeruli has something to do with the degeneration of tubules and not glomeruli.

Lipoid-containing Cells in the Spleen in Diabetes with Lipemia.—WARREN and ROOT (*Am. J. Path.*, 1926, **2**, 69) report 3 cases of diabetes mellitus with large lipoid containing cells in the spleen and compare these with 8 others collected from the literature. Lipemia was present in all but 1 case. In the spleen this lipoid material, as judged by staining reactions, varied in its chemical constitution, seeming to consist usually of cholesterol esters and related substances or phosphatids. Fatty acids and soaps possibly were also present. The reticuloendothelium system seems to be involved in lipoid metabolism, and may perhaps selectively absorb cholesterol compounds, etc. Besides the spleen there seems to be a definite relation between arteriosclerosis and lipemia. All cases showed marked vascular change, atheromata and fatty streaks. It is possible the general cachectic state of the tissues in diabetes with lipemia may predispose atheromatous degeneration in the intima of the arteries.

HYGIENE AND PUBLIC HEALTH

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The Immunity Produced by the Growth of Tetanus Bacilli in the Digestive Tract.—TENBROECK and BAUER (*Proc. Soc. Exp. Biol. and Med.*, 1923–1924, **21**, 267) have previously shown that soon after tetanus bacilli are fed to guinea pigs agglutinins for the type fed appear in the blood, and that even after six months the agglutinins remain specific. Antitoxin appears more slowly, but by the end of six months it amounts to about 0.05 U. S. A. units per cubic centimeter of serum. This is not a high content if one thinks of units, but it will neutralize a considerable amount of toxin. Assuming that this antitoxin would render the animals immune to tetanus bacilli as at the beginning of their experiments, the authors regarded antitoxin as an adequate protecting antibody. The results given in the present paper (*J. Exper. Med.*, 1926, **43**, 361) show this assumption not to be justified for, while the guinea pigs are shown to be immune to the type organisms fed, they are just as susceptible to organisms of other types as are control animals. The authors believe that antitoxin plays little part in acquired immunity to tetanus, but that there are other bodies, specific for type, which protect animals against infection. Guinea pigs can be made immune to more than one type of tetanus bacilli if these types are growing in the digestive tract. The number of types of these organisms which could be isolated from the stool of a single human was never determined, but examination of the sera of many individuals in Peking shows that most of them have agglutinins for several types of bacilli. This, together with the many chances for the introduction of tetanus spores into the digestive tracts, makes it seem that man must often carry the common types and that he thereby acquires an immunity. Carrying the bacillus does not necessarily make man absolutely immune, for in 2 cases of infection in individuals tetanus bacilli were obtained from the stools. In 1 of these cases the organism in the stool was of the same serologic type as that producing the infection. In the other case infection followed a rupture of the intestines and it was not possible to recover the bacillus responsible for the tetanus. It is worthy of note that both cases recovered while of 4 cases whose stools contained no tetanus bacilli, 3 died in spite of intensive treatment with antitoxin. While these findings seem suggestive, the authors do not wish to draw conclusions from so few cases, and it will be some time before enough data can be secured to warrant any conclusions as to the protection afforded man by tetanus bacilli in the intestinal canal of man. Inci-

dentally it may be mentioned that it has not been possible to detect any ill effects due to the presence of these organisms in the digestive tract. Although the tetanus bacillus is known to form an hemolysin, blood counts have failed to show an anemia in carrier animals; observations are of accord with the statement of Rabinowitsch (*Arch. Hyg.*, 1907, **61**, 103) that marasmus and death resulted from feeding this organism. The authors describe in their article a method for the production of tetanus by the injection of a fixed number of spores, together with tests made in selecting animals for experimental work. Guinea pigs fed a single serologic type of tetanus bacilli will, after six months, show considerable amounts of antitoxin in their sera and will manifest immunity to the type fed. To other types they are just as susceptible as are controls. Animals fed several types are immunized to each of these types. It is pointed out in the discussion that the digestive tract of man may carry several types and that he probably reacts in a manner resembling the guinea-pig carriers. Guinea pigs that carry tetanus bacilli and have antitoxin in their sera show little if any resistance to tetanus toxin As there is no relation between the amount of antitoxin in the blood and immunity to tetanus, the authors believe that other bodies, specific for type, must occur and make for the immunity observed.

An Experimental Investigation of the Supposed Relation between Good Physical Condition and Natural Resistance to Infection.—Spaeth (*Am. J. Hyg.*, 1925, **5**, 839) states that he found female white rats which are in good physical condition (training) as a result of daily spontaneous exercise, survived intraperitoneal infections of Type I pneumococcus less well than do unexercised control rats. Good physical condition may, therefore, be said not to increase the resistance of white rats to infection. The evidence presented suggests that the increase in natural resistance to infection, following forced exercise to exhaustion, as previously reported by Oppenheimer and Spaeth and by Nicholls and Spaeth, cannot be correlated with the good physical condition of the exhausted animals. Guinea pigs, on a reduced diet, that have suffered a weight loss equivalent to the weight lost by forced running, resisted intraperitoneal infections of Type I pneumococcus better than did normally fed pigs. Young starved guinea pigs (150 to 300 gm.) and exhausted pigs of similar weight were physiologically comparable insofar as both groups, when infected with Type I pneumococcus and fed immediately thereafter, resisted infection better than do normally fed control pigs. The starvation experiments indicated that in exhausted guinea pigs increased resistance to infection is, in some at present unexplained way, related to the weight recovery process, and has nothing to do with fatigue nor with fatigue products. The greater resistance to infection of both starved and exhausted guinea pigs suggests that natural resistance is in no sense a static matter, but is in part, at least, a function of anabolic rate. The relation between natural resistance and anabolism in man has long been recognized in the treatment of pulmonary tuberculosis. It is also well known that diabetics—in whom the anabolic rate is reduced to a minimum—are particularly susceptible to infection.

PHYSIOLOGY.

UNDER THE AUSPICES OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA.

The Physiology of Urine Formation.—J. M. HAYMAN (from the Department of Pharmacology, University of Pennsylvania Medical School). In 1917 Cushny suggested that many apparent contradictions in the two major theories of kidney function, filtration reabsorption and secretion, might be harmonized by assuming that a protein-free fluid, containing all the diffusible substances of the plasma, is filtered from the blood in the glomerulus, and that this filtrate is elaborated as it passes down the tubule by the reabsorption of water and certain substances useful for the organism (threshold bodies), leading to the concentration of others (no-threshold bodies) in the urine. The fluid reabsorbed was at first assumed to have about the composition of Locke's solution. Mayrs'[1] calculations, however, soon made it necessary to include in the reabsorbed fluid small amounts of urea and possibly some other constituents of plasma, and to assume that at least under certain conditions it might vary greatly in composition. This theory consists of two distinct processes, differing in nature as well as site—glomerular filtration, which is purely physical, and tubular reabsorption, which depends upon the vital activity of the tubule cells. Recent experiments bearing on this hypothesis will be cited.

Evidence for Filtration Reabsorption. The perfusion experiments of Richards and Plant[2] showed that changes in renal blood pressure, without change in volume flow of blood, produce corresponding changes in the rate of urine formation. At the time they were made these experiments were the most direct evidence in support of a filtration hypothesis. By a similar method Dreyer and Verney[3] obtained similar results. Hayman[4] has shown that in the frog the blood pressure in the glomerular capillaries is sufficiently high to furnish the energy necessary for filtration. Wearn and Richards[5] succeeded in introducing a fine capillary into Bowman's space in the frog's kidney, collecting the glomerular fluid and subjecting it to analysis. It was found to be protein free and to contain chlorid and glucose at a time when bladder urine was free from each of these. These experiments contain incontestable proof of reabsorption within the tubule and lend support to the conception that glomerular function is physical rather than vital or secretory. White and Schmitt[6] have confirmed these results in the kidney of Necturus, where the reabsorption of sugar and chlorid occurs in the proximal convoluted tubule.

Other substances found in the glomerular fluid of frogs are urea, potassium, and, after injection, foreign substances such as dyes and iron salts. Quantitative estimation of the chlorid content of glomerular fluid and plasma in some instances is in accord with the filtration theory; exceptions encountered, however, indicate that filtration as at present defined may be inadequate, and emphasize the need for study of the way in which capillary forces and the vitality of the glomerular membrane influence the filtration process.[7] Bieter and Hirschfelder[8] have also watched the passage of dyes through the glomerular membrane in the frog's kidney. Clark[9] perfused the frog's kidney both

through the aorta and renal portal systems, and found that the amounts of glucose in the urine depended on the glucose concentration of the fluid bathing the tubules and not upon that of the arterial perfusate. De Haan and Bakker,[10] however, believe that the glomerular fluid may contain protein which is absorbed in the tubule. Mayrs and Watt[11] estimate that the proportion of the fluid of the blood which is filtered through the capsule varies from 6 to 40 per cent; Rehberg[12] believes that filtration of as much as 200 cc. per minute is possible in the human kidneys.

Evidence for Tubular Secretion. It is a moot question at the present time whether filtration and reabsorption are sufficient to account for the formation of urine, or whether specific secretion by the tubule cells is an additional factor. Heidenhain based his argument for tubular secretion largely on the appearance of dyes within the cells of the convoluted tubules. Much of this evidence has been discredited by the studies of Dawson,[13] von Möllendorff,[14] Mitamura,[15] Hayman[16] and others. When a stain is introduced directly into the capsular fluid histologic sections of the convoluted tubules present the same appearance as those obtained when the dye reaches the kidney by way of the blood stream. Grollman,[17] Edwards[18] and Schulten[19] have cautioned, however, that each dye or group must be studied separately. Marshall and Vickers,[20] finding that when the blood pressure is reduced in dogs, so that no urine is eliminated, there is a great accumulation of phenol red in the cortex of the kidney, and, having determined that under some conditions more dye is eliminated in the urine than is brought to the kidneys by the blood during the same time, conclude that part of the phenol red is secreted by the cells of the convoluted tubules after a preliminary concentration in them. Starling and Verney,[21] using a heart-lung-kidney preparation, found that after the addition of cyanid to the blood (which they assumed affected only the function of the tubules) the elimination of phenol red, urea and sulphate diminished, while that of water and chlorid increased. They interpreted this as indicating that these substances are in part secreted. In a later paper, however, Eichholtz and Starling[22] admit that cyanid is not without effect on the glomerular membrane, and it seems that increased permeability of the glomerulus to water and chlorid would go far toward explaining their results. Mayrs[23] believes that uric acid must be secreted by the fowl's kidney; Marshall and Crane,[24] that creatinine is secreted in the dog's kidney and urea and in the amphibian, but not in the mammalian.

More indirect evidence of the secretion of various substances has been presented by Yoshida,[25] White,[26] Underhill[27] and others.

Regulation of Urine Formation. Richards and Schmidt[28] found by microscopic observation of the frog's kidney that the number of glomeruli through which blood flowed varied under different conditions, and that flow through individual capillaries of a single glomerulus also varied. Similar observations by indirect means have been made on the mammalian kidney by Khanolkar[29] and by Hayman and Starr.[30] Changes in intraglomerular pressure may also be produced by changes in the relative constriction of afferent and efferent vessel without any alteration in arterial blood pressure. Hayman[4] found that under the action of adrenalin and caffein changes in glomerular capillary pressure might be produced which were quite out of proportion to the effect on aortic pressure.

Among the many experiments on the chemical regulation of urinary secretion those on the action of pituitary extract are perhaps the most fascinating. Its diuretic action in the anesthetized animal and its antidiuretic action, particularly in the presence of a diuresis, in the intact animal are well known. The belief that the former may arise from slight constriction of the efferent glomerular vessels, the latter from stronger constriction, retarding flow, or from constriction of the afferent vessel, finds support in the observation of Stehle and Bourne[31] that, as the antidiuretic effect passes off the urine contains protein. Most observers, however, believe that the antidiuretic action is brought about by direct action on the tubule cells (Craig,[32] Miura,[33] Macfarlane[34]). Starling and Verney found that the addition of pituitary extract to the blood in their heart-lung-kidney preparation increased the concentration of chlorid in the urine. Brull and Eichholtz[35] report that removal of the pituitary gland or injury to surrounding structures diminishes the elimination of phosphate and chlorid in anesthetized dogs, while Addis[36] and his associates found that pituitary injection diminished the elimination of urea.

Nephritis. The influence of current physiologic views is evident in some recent papers dealing with the secretion of abnormal urine and with nephritis. That albumin is eliminated chiefly by the glomerulus has been evident since Posner's writings. Starr[37] has shown that albuminuria can be induced experimentally by vasoconstrictor agents which may be thought to lead to asphyxia and hence to increased permeability of the glomerulus; among such agents are CO_2 by inhalation, adrenalin, ephedrin, fright. Toxins undoubtedly may similarly increase the permeability of the capsule. It is not unlikely from the experiments of Kellaway, Davies and Williams[38] that in addition there is an exudation of lymph from the damaged tubules, as from other denuded surfaces. Dunn[39] and his pupils believe that the changes in the urine found in experimental nephritis can be explained by assuming that the damaged tubular epithelium has lost its discriminating power, so that the reabsorbed fluid contains more of the relatively unabsorbable bodies. The more deficient tubular function becomes, the more the character of the fluid reabsorbed depends on simple diffusion rather than on the vital activity of the epithelial cells. Rehberg believes that "back diffusion" of no-threshold substances occurs even in the normal kidney, and that it explains the varying concentration ratios of low-threshold bodies without necessitating tubular secretion.

Mayrs[40] has presented a classification of nephritis in accord with the "modern theory." The hydremic type, he suggests, results from a primary injury to the glomerulus, leading to increased permeability and loss of serum protein, which results in a decrease in the total colloid osmotic pressure of the plasma. Disturbance of the normal relationship between capillary blood pressure and colloid osmotic pressure leads to edema. In the azotemic type, although many glomerular-tubule units are not functioning, the rise in blood urea may be ascribed to damaged tubule cells reabsorbing some urea along with chlorid, in the effort to conserve the latter, since the cells seem unable to concentrate the urine beyond a low degree.

Many recent papers have had to be omitted because of lack of space. More detailed discussion of the problems of the secretion of urine and extensive bibliographies are presented in Marshall's[41] review and Cushny's[42] monograph.

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